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Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet international spécifiée à la page suivante.

Den Haag, den
The Hague,
La Haye, le 25. 04. 2005

Der Präsident des Europäischen Patentamts
Im Auftrag
For the President of the European Patent Office
Le Président de l'Office européen des brevets
p.o.

S. Aulbers

Patentanmeldung Nr.
Patent application no.
Demande de brevet n°

PCT/EP 04/002492

Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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Anmelder:
Applicant(s):
Demandeur(s): 1. ACTELION PHARMACEUTICALS LTD - Allschwil, Switzerland

Bezeichnung der Erfindung:
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Titre de l'invention: INDOL-1-YL-ACETIC ACID DERIVATIVES

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Indol-1-yl-acetic acid derivatives

Field of the invention:

The present invention relates to indol-1-yl-acetic acid derivatives and their use as potent "chemoattractant receptor-homologous molecule expressed on Th2 cells" (hereinafter called CRTH2) antagonists in the treatment of prostaglandin mediated diseases, to pharmaceutical compositions containing these derivatives and to processes for their preparation. In particular, at least one of such derivatives of the general Formula I may be used in pharmaceutical compositions for the treatment of both chronic and acute allergic/immune disorders comprising allergic asthma, rhinitis, chronic obstructive pulmonary disease (COPD), dermatitis, inflammatory bowel disease, rheumatoid arthritis, allergic nephritis, conjunctivitis, atopic dermatitis, bronchial asthma, food allergy, systemic mast cell disorders, anaphylactic shock, urticaria, eczema, itching, inflammation, ischemia-reperfusion injury, cerebrovascular disorders, pleuritis, ulcerative colitis, eosinophil-related diseases, such as Churg-Strauss syndrome and sinusitis, basophil-related diseases, such as basophilic leukemia and basophilic leukocytosis in humans and other mammals.

The invention also relates to novel compounds of Formula II which may also be used in pharmaceutical compositions as outlined above.

Background of the invention:

Prostaglandin D2 is a known agonist of the thromboxane A2 (TxA2) receptor, the PGD2 (DP) receptor and the recently identified G-protein-coupled "chemoattractant receptor-homologous molecule expressed on Th2 cells" (CRTH2).

The response to allergen exposure in a previously sensitized host results in a cascade effect involving numerous cell types and release of a number of cytokines, chemokines, and multiple mediators. Among these critical initiators are the cytokines interleukin (IL)-4, IL-13, and IL-5, which play critical roles in Th2 cell differentiation, immunoglobulin (Ig)E synthesis, mast cell growth and differentiation, upregulation of CD23 expression, and the differentiation, recruitment, and activation of eosinophils. The stimulated release of the array of mediators, causes end-organ damage, including constriction and hyperresponsiveness, vascular permeability, edema, mucous secretion, and further inflammation.

Because of the number of responses targeted, corticosteroids have proven to be the most effective therapy. Rather than antagonizing these specific responses in a directed way, another approach is to alter the immune response, that is, to change the nature of the immunological response to allergen. CRTH2 is preferentially expressed on Th2 cells and is a chemoattractant receptor for PGD2 that mediates PGD2-dependent migration of blood Th2 cells. Chemoattractants are responsible for the recruitment of both Th2 cells and other effector cells of allergic inflammation and may provide the conceptual basis for the development of new therapeutic strategies, especially in allergic conditions.

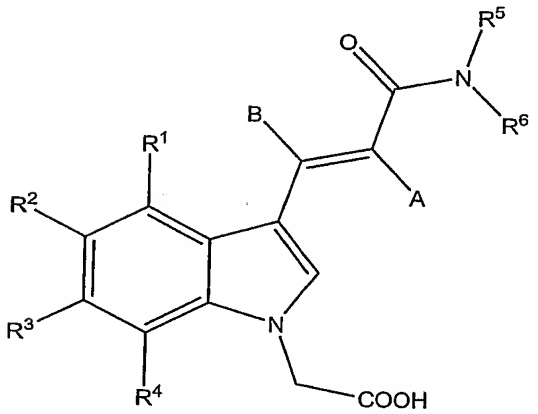
So far, few compounds having CRTH2 antagonistic activity have been reported in the patent literature. Bayer AG claims in GB Patent Specification No. 2388540 the use of Ramatroban ((3R)-3-(4-fluorobenzene-sulfonamido)-1,2,3,4-tetrahydrocarbazole-9-propionic acid) for the prophylaxis and treatment of allergic diseases, such as asthma, allergic rhinitis or allergic conjuvatitis Further, (2-tert.-butoxycarbonyl-1, 2, 3, 4-tetrahydro-pyrido[4,3-b]indol-5-yl)-acetic acid and (2-ethoxycarbonyl-1, 2, 3, 4-

tetrahydro-pyrido[4,3-b]indol-5-yl)-acetic acid are disclosed by Kyle F. et *al* in two patent specifications i.e. in US 5817756 and WO 9507294, respectively.

Furthermore, a certain oral bioavailability of Ramatroban and its ability to inhibit prostaglandin D2-induced eosinophil migration *in vitro* has been reported in *Journal of Pharmacology and Experimental Therapeutics*, **305(1)**, p.347-352 (2003).

Description of the invention:

In a first aspect the present invention relates to pharmaceutical compositions containing at least one compound of the indol-1-yl-acetic acids of the general Formula I



I

wherein

A represents hydrogen; lower alkyl; halogen or cyano;

B represents hydrogen; lower alkyl or halogen;

R^1, R^2, R^3 and R^4 independently represent hydrogen; lower alkyl; halogen; nitro; cyano or formyl;

R^5 and R^6 independently represent hydrogen; lower alkyl; lower alkenyl; aryl; lower alkoxy-aryl; lower alkoxycarbonyl-aryl; lower alkylcarbonyl-aryl; aryl-lower alkoxy-aryl; aryl-lower alkyl; aryl-lower alkyl-aryl; arylcarbonyl-aryl; aryloxy-aryl; whereby the aryl group is unsubstituted or mono- or di-substituted with lower alkyl, lower alkoxy, halogen, cyano, lower alkoxycarbonyl, lower alkylcarbonyl, phenyl, benzyl, benzoyl, benzyloxy, benzyloxycarbonyl, trifluormethyl or trifluormethoxy; cyclolalkyl or heteroaryl;

R^5 and R^6, together with the nitrogen atom to which they are attached, form a heterocyclic ring system;

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, meso forms, geometric isomers,

prodrugs of compounds in which a prodrug forming group is present, as well as solvates and morphological forms, pharmaceutically acceptable salts thereof and usual inert carrier materials or adjuvants.

The compounds of the general Fomula I are CRTH2 receptor antagonists and may be used for the prevention and treatment of chronic and acute allergic immune disorders comprising allergic asthma, rhinitis, chronic obstructive pulmonary disease (COPD), dermatitis, inflammatory bowel disease, rheumatoid arthritis, allergic nephritis, conjunctivitis, atopic dermatitis, bronchial asthma, food allergy, systemic mast cell disorders, anaphylactic shock, urticaria, eczema, itching, inflammation, ischemia-reperfusion injury, cerebrovascular disorders, pleuritis, ulcerative colitis, eosinophil-related diseases comprising Churg-Strauss syndrome and sinusitis, basophil-related diseases, comprising basophilic leukemia and basophilic leukocytosis in humans and other mammals.

Another aspect of the present invention is the use of compounds of the general Formula I as medicaments to treat the aforementioned diseases. In this respect the use of the following compounds is particularly preferred:

[3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;

[3-((E)-2-cyano-2-m-tolylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
{3-[(E)-2-cyano-2-(4-methoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(3-bromo-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(cyclohexylmethyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-phenethylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
[3-((E)-2-cyano-2-isopropylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
[3-((E)-2-cyano-2-propylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
[3-((E)-2-cyano-2-cyclohexylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
{3-[(E)-2-cyano-2-(3-methyl-butylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-benzylcarbamoyl-2-cyano-vinyl)-indol-1-yl]-acetic acid;
{3-[(E)-2-(benzyl-phenyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-cyano-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-o-tolylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
{3-[(E)-2-cyano-2-(4-ethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-fluoro-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-phenoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(naphthalen-2-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(2-isopropyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-p-tolylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
{3-[(E)-2-cyano-2-(4-isopropyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3-methoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3-fluoro-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(9H-fluoren-2-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-propyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(biphenyl-4-ylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3,2'-dimethyl-biphenyl-4-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-tert-butyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(2-benzyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-butyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(2-acetyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(indan-5-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-sec-butyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-ethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3-ethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(2-propyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3-phenoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3-ethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(2-ethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(3-benzyloxy-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-bromo-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-iodo-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3-iodo-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
(3-{(E)-2-cyano-2-[(4-fluoro-phenyl)-methyl-carbamoyl]-vinyl}-indol-1-yl)-acetic acid;
(3-{(E)-2-cyano-2-[(4-methoxy-phenyl)-methyl-carbamoyl]-vinyl}-indol-1-yl)-acetic acid;
{3-[(E)-2-cyano-2-(methyl-phenyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-3-(3,4-dihydro-2H-quinolin-1-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(methyl-p-tolyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;
(3-{(E)-2-cyano-2-[2-(2,4-dichloro-phenoxy)-phenylcarbamoyl]-vinyl}-indol-1-yl)-acetic acid;
{3-[(E)-2-cyano-2-(2,5-dimethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(9-ethyl-9H-carbazol-3-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(3,5-bis-trifluoromethyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(5-methoxy-2-methyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(3-benzoyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-benzyloxy-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3-nitro-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(9-oxo-9H-fluoren-2-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(4-methoxy-biphenyl-3-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(2-methoxy-dibenzofuran-3-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(9-oxo-9H-fluoren-4-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(9-oxo-9H-fluoren-1-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(2-benzoyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(3-chloro-4-methoxy-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(5-chloro-2-methoxy-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
3-[(E)-3-(1-carboxymethyl-1H-indol-3-yl)-2-cyano-acryloylamino]-4-methyl-benzoic acid methyl ester;
{3-[(E)-2-(4-chloro-2-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
2-[(E)-3-(1-carboxymethyl-1H-indol-3-yl)-2-cyano-acryloylamino]-benzoic acid methyl ester;
{3-[(E)-2-cyano-2-(4-trifluoromethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3,5-dimethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(3-bromo-4-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-bromo-3-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
4-[(E)-3-(1-carboxymethyl-1H-indol-3-yl)-2-cyano-acryloylamino]-benzoic acid ethyl ester;
3-[(E)-3-(1-carboxymethyl-1H-indol-3-yl)-2-cyano-acryloylamino]-benzoic acid methyl ester;
{3-[(E)-2-cyano-2-(4-trifluoromethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3,5-dimethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-bromo-3-chloro-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-bromo-2-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-acetyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(2-bromo-4-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(benzo[1,3]dioxol-5-ylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(2,3-dihydro-benzo[1,4]dioxin-6-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(2-methoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(2-phenoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(phenethyl-phenyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-3-(11,12-dihydro-6H-dibenzo[b,f]azocin-5-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid;

[3-((E)-2-cyano-2-diphenylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;

sodium [3-((E)-2-cyano-3-dibenzo[b,f]azepin-5-yl-3-oxo-propenyl)-indol-1-yl]-acetate

(3-{(E)-2-[(4-chloro-phenyl)-methyl-carbamoyl]-2-cyano-vinyl}-indol-1-yl)-acetic acid;

{3-[(E)-2-cyano-3-(6,11-dihydro-dibenzo[b,e]azepin-5-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid;

[3-((E)-2-cyano-2-diphenethylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;

{3-[(E)-2-cyano-3-(10,11-dihydro-dibenzo[b,f]azepin-5-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid;

(3-{(E)-2-cyano-2-[methyl-((R)-1-phenyl-ethyl)-carbamoyl]-vinyl}-indol-1-yl)-acetic acid;

{3-[(E)-2-(benzyl-methyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

(3-{(E)-2-[(4-acetyl-phenyl)-methyl-carbamoyl]-2-cyano-vinyl}-indol-1-yl)-acetic acid;

(3-{(E)-2-[(4-acetyl-phenyl)-furan-2-ylmethyl-carbamoyl]-2-cyano-vinyl}-indol-1-yl)-acetic acid;

{3-[(E)-2-(benzyl-carboxymethyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

3-{benzyl-[(E)-3-(1-carboxymethyl-1H-indol-3-yl)-2-cyano-acryloyl]-amino}-propionic acid;

{3-[(E)-2-cyano-3-(2,3-dihydro-indol-1-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-(carboxymethyl-phenyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

(3-{(E)-2-cyano-2-[(2-cyano-ethyl)-phenyl-carbamoyl]-vinyl}-indol-1-yl)-acetic acid;

(3-{(E)-2-[(3-chloro-phenyl)-methyl-carbamoyl]-2-cyano-vinyl}-indol-1-yl)-acetic acid;

{3-[(E)-2-(allyl-phenyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

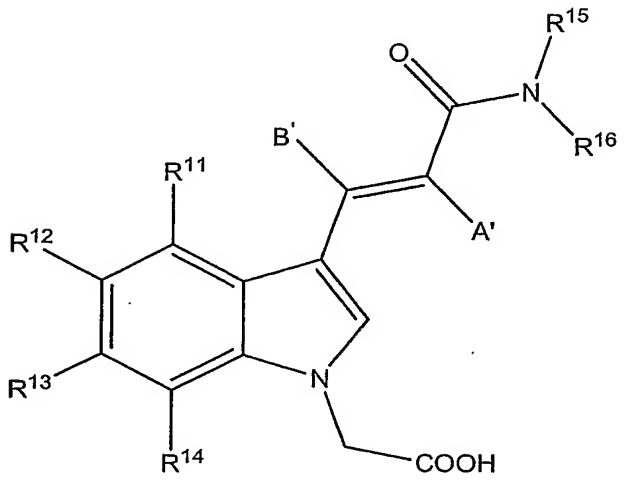
{3-[(E)-2-cyano-2-(cyclohexyl-phenyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(methyl-o-tolyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(ethyl-phenyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(butyl-phenyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
[5-bromo-3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
[3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-7-methyl-indol-1-yl]-acetic acid;
[3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-5-fluoro-indol-1-yl]-acetic acid;
[3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-6-fluoro-indol-1-yl]-acetic acid;
[3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-6-nitro-indol-1-yl]-acetic acid;
[3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-5-methyl-indol-1-yl]-acetic acid.

Compounds of the above general Formula I are novel, with the exception of the following compounds which, however, are also potent CRTH2 receptor antagonists and in this respect are not described in the literature:
{3-[(E)-2-cyano-2-(4-fluoro-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-m-tolylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
{3-[(E)-2-(3-bromo-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
[3-((E)-2-benzylcarbamoyl-2-cyano-vinyl)-indol-1-yl]-acetic acid;
[3-((E)-2-cyano-2-o-tolylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
[3-((E)-2-cyano-2-p-tolylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
{3-[(E)-2-(4-bromo-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-ethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-methoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-ethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-isopropylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
{3-[(E)-2-cyano-2-(3-ethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-3-[[2-(1H-indol-3-yl)ethyl]amino]-3-oxo-1-propenyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-chloro-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid.

An especially preferred embodiment of the present invention are the novel compounds of the general Formula II



II

wherein

A' represents hydrogen; lower alkyl; halogen or cyano;

B' represents hydrogen; lower alkyl or halogen;

R^{11}, R^{12}, R^{13} and R^{14} independently represent hydrogen; lower alkyl; halogen; nitro; cyano or formyl;

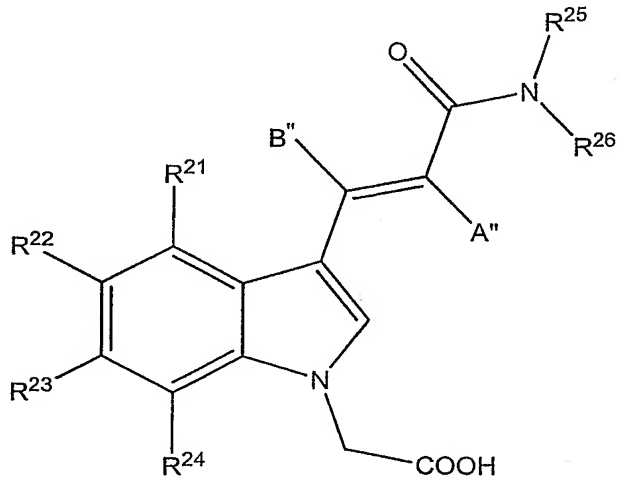
R^{15} and R^{16} independently represent hydrogen; lower alkyl; lower alkenyl; aryl; lower alkoxy-aryl; lower alkoxycarbonyl-aryl; lower alkylcarbonyl-aryl; aryl-lower alkoxy-aryl; aryl-lower alkyl; aryl-lower alkyl-aryl; arylcarbonyl-aryl; aryloxy-aryl; whereby the aryl group is unsubstituted or mono- or di-substituted with lower alkyl, lower alkoxy, halogen, cyano, lower alkoxycarbonyl, lower alkylcarbonyl, phenyl, benzyl, benzoyl, benzyloxy, benzyloxycarbonyl, trifluormethyl or trifluormethoxy; cyclolalkyl or heteroaryl;

R^{15} and R^{16}, together with the nitrogen atom to which they are attached, form a heterocyclic ring system;

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, meso forms, geometric isomers,
prodrugs of compounds in which a prodrug forming group is present, as well as solvates and morphological forms and pharmaceutically acceptable salts thereof ;
with the proviso that the substituents R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} all at the same time do not represent hydrogen or in addition and in case either one of the substituents R^{15} or R^{16} represents hydrogen and the other aryl then the aryl group is not an unsubstituted indol-3-yl-ethyl, benzyl, or phenyl group, and also not a C1-C3 alkyl, C1-C2 alkoxy or halogen mono-substituted phenyl group, or R15 and R16 together with the nitrogen atom to which they are attached do not form a. phenyl substituted piperazine ring.

In a particular aspect the present invention thus relates to these novel compounds per se as well as to their use as pharmaceutically active ingredients; in addition these novel compounds relate also to pharmaceutical compositions containing one or several of these novel compounds;
to the use of these novel compounds as CRTH2 antagonists for the prevention and/or treatment of chronic and acute allergic immune disorders comprising allergic asthma, rhinitis, chronic obstructive pulmonary disease (COPD), dermatitis, inflammatory bowel disease, rheumatoid arthritis, allergic nephritis, conjunctivitis, atopic dermatitis, bronchial asthma, food allergy, systemic mast cell disorders, anaphylactic shock, urticaria, eczema, itching, inflammation, ischemia-reperfusion injury, cerebrovascular disorders, pleuritis, ulcerative colitis, eosinophil-related diseases, such as Churg-Strauss syndrome and sinusitis, basophil-related diseases, such as basophilic leukemia and basophilic leukocytosis in humans and other mammals

Particularly preferred are novel compounds of the general Formula III,



III

wherein

A'' represents hydrogen; methyl; trifluoromethyl; chloro; or cyano;

B'' represents hydrogen; methyl; trifluoromethyl; or chloro;

R^{21}, R^{22}, R^{23} and R^{24} represent independently hydrogen; lower alkyl; halo-lower alkyl; lower alkoxy; halogen; nitro; cyano or formyl;

R^{25} and R^{26} represent independently hydrogen, lower alkenyl, alkoxy-aryl, alkoxycarbonyl-aryl, lower alkyl, alkylcarbonyl-aryl, arylalkoxy-aryl, arylalkyl, arylalkyl-aryl, aryl, arylcarbonyl-aryl, aryloxy-aryl, cyclolalkyl, heteroaryl;

R^{25} and R^{26}, together with the nitrogen atom to which they are attached, form a heterocyclic ring system with 3 to 15 ring atoms;

R^{25} represents hydrogen; lower alkyl; or arylalkyl; and

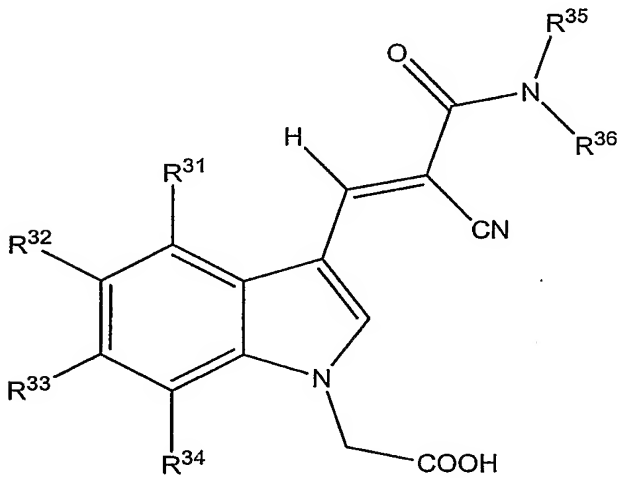
R^{26} represents lower alkyl; alkoxy-aryl; alkoxycarbonyl-aryl; alkylcarbonyl-aryl; arylalkoxy-aryl; arylalkyl; arylalkyl-aryl; arylcarbonyl-aryl; aryloxy-aryl; cyclylalkyl.

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, meso forms, geometric isomers,

prodrugs of compounds in which a prodrug forming group is present, as well as solvates and morphological forms and pharmaceutically acceptable salts thereof ;

with the proviso that the substituents R^{21}, R^{22}, R^{23}, R^{24}, R^{25} and R^{26} all at the same time do not represent hydrogen or in addition and in case either one of the substituents R^{25} or R^{26} represents hydrogen and the other aryl then the aryl group is not an unsubstituted indol-3-yl-ethyl, benzyl, or phenyl group, and also not a C1-C3 alkyl, C1-C2 alkoxy or halogen mono-substituted phenyl group, or R^{25} and R^{26} together with the nitrogen atom to which they are attached do not form a. phenyl substituted piperazine ring.

In another aspect, R^{25} and R^{26}, together with the nitrogen atom to which they are attached, may form a heterocyclic ring system with 3 to 15 ring atoms and this preferred aspect encompasses novel compounds of Formula IV



IV

wherein

R^{31}, R^{32}, R^{33} and R^{34} represent independently methyl; trifluoromethyl; methoxy; fluoro, chloro;

R^{35} and R^{36}, together with the nitrogen atom to which they are attached, form a acridine, azepine, azocine, carbazole, indole, phenanthiridine or quinoline ring; or

R^{35} represents hydrogen,

R^{36} represents 2-ethoxy-phenyl; 2-methoxycarbonyl-phenyl, 2-methyl-5-methoxycarbonyl-phenyl, 3-methoxycarbonyl-phenyl, 4-ethoxycarbonyl-phenyl; 3-methyl-butyl, propyl; 2-acetyl-phenyl, 4-acetyl-phenyl; 3-benzyloxy-phenyl, 4-benzyloxy-phenyl; benzyl, phenethyl; 2-benzyl-phenyl; 2-benzoyl-phenyl, 3-benzoyl-phenyl; 2,3-dihydro-benzo[1,4]dioxin-6-yl, 2,5-dimethyl-phenyl, 2-bromo-4-methyl-phenyl, 2-isopropyl-phenyl, 2-methoxy-dibenzofuran-3-yl, 2-methoxy-phenyl, 2-propyl-phenyl, 3,2'-dimethyl-biphenyl-4-yl, 3,5-bis-trifluoromethyl-phenyl, 3,5-dimethoxy-phenyl, 3,5-dimethyl-phenyl, 3-bromo-4-methyl-phenyl, 3-bromophenyl, 3-chloro-4-methoxy-phenyl, 3-ethyl-phenyl, 3-fluoro-phenyl, 3-iodo-phenyl, 3-methoxy-phenyl, 3-nitro-phenyl, 4-bromo-2-methyl-phenyl, 4-bromo-3-chloro-phenyl, 4-bromo-3-methyl-phenyl, 4-butyl-phenyl, 4-chloro-2-methyl-phenyl, 4-cyano-phenyl, 4-iodo-phenyl, 4-isopropyl-phenyl, 4-methoxy-biphenyl-3-yl, 4-propyl-phenyl, 4-sec-butyl-phenyl, 4-tert-butyl-phenyl, 4-trifluoromethoxy-phenyl, 4-trifluoromethyl-phenyl, 5-chloro-2-methoxy-phenyl, 5-methoxy-2-methyl-phenyl, 9-ethyl-9H-carbazol-3-yl, 9H-fluoren-2-yl, 9-oxo-9H-fluoren-1-yl, 9-oxo-9H-fluoren-2-yl, 9-oxo-9H-fluoren-4-yl, benzo[1,3]dioxol-5-yl, biphenyl-4-yl, indan-5-yl, naphthalen-2-yl; 2,4-dichloro-phenoxy)-phenyl, 2-phenoxy-phenyl, 3-phenoxy-phenyl, 4-phenoxy-phenyl; cyclohexylmethyl; or

R^{35} represents methyl; and R^{36} represents 4-acetyl-phenyl; (R)-1-phenyl-ethyl, benzyl; 3-chloro-phenyl; 4-chloro-phenyl; 4-fluoro-phenyl; 4-methoxy-phenyl; o-tolyl; m-tolyl or p-tolyl;

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, meso forms, geometric isomers,

prodrugs of compounds in which a prodrug forming group is present, as well as solvates and morphological forms and pharmaceutically acceptable salts thereof ;

In a further preferred embodiment of the compounds of Formula IV independently the substituents R^{35} represent phenyl; and

R^{36} represent allyl; 2-cyano-ethyl; butyl; carboxymethyl; ethyl; benzyl; phenethyl; phenyl; cyclohexyl.

In another aspect, the substituents R^{35} and R^{36}, together with the nitrogen atom to which they are attached form a acridine; azepine; azocine; carbazole; indole; phenanthiridine; or quinoline ring; preferably 5,6-dihydro-phenanthridine; 9,10-dihydro-acridine; 5,6-dihydro-dibenzo[b,f]azocine; 10,11-dihydro-dibenzo[b,f]azepine; 11,12-dihydro-6H-dibenzo[b,f]azocine; 2,3-dihydro-indole; 3,4-dihydro-2H-quinoline; 6,11-dihydro-dibenzo[b,e]azepine; dibenzo[b,f]azepine ring.

Most preferred novel compounds of the present invention include, but are not limited to:
sodium [3-((E)-2-cyano-3-dibenzo[b,f]azepin-5-yl-3-oxo-propenyl)-indol-1-yl]-acetate;
{3-[(E)-2-(allyl-phenyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(phenethyl-phenyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(butyl-phenyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
(3-{(E)-2-cyano-2-[(2-cyano-ethyl)-phenyl-carbamoyl]-vinyl}-indol-1-yl)-acetic acid;
{3-[(E)-2-cyano-3-(10,11-dihydro-dibenzo[b,f]azepin-5-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid;
(3-{(E)-2-cyano-2-[(4-fluoro-phenyl)-methyl-carbamoyl]-vinyl}-indol-1-yl)-acetic acid;
{3-[(E)-2-cyano-2-(ethyl-phenyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-3-(6,11-dihydro-dibenzo[b,e]azepin-5-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(cyclohexyl-phenyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;
(3-{(E)-2-[(4-chloro-phenyl)-methyl-carbamoyl]-2-cyano-vinyl}-indol-1-yl)-acetic acid;
(3-{(E)-2-cyano-2-[(4-methoxy-phenyl)-methyl-carbamoyl]-vinyl}-indol-1-yl)-acetic acid;
{3-[(E)-2-cyano-2-(methyl-o-tolyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-diphenethylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
(3-{(E)-2-[(4-acetyl-phenyl)-furan-2-ylmethyl-carbamoyl]-2-cyano-vinyl}-indol-1-yl)-acetic acid;
(3-{(E)-2-[(4-acetyl-phenyl)-methyl-carbamoyl]-2-cyano-vinyl}-indol-1-yl)-acetic acid;

{3-[(E)-2-cyano-3-(3,4-dihydro-2H-quinolin-1-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid.

Particularly preferred novel compounds of the present invention include

{3-[(E)-2-cyano-2-(methyl-phenyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;

(3-{(E)-2-[(3-chloro-phenyl)-methyl-carbamoyl]-2-cyano-vinyl}-indol-1-yl)-acetic acid;

{3-[(E)-2-(carboxymethyl-phenyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-(benzyl-phenyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-(3-benzoyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(2-ethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(4-methoxy-biphenyl-3-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

[3-((E)-2-cyano-2-diphenylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;

(3-{(E)-2-cyano-2-[2-(2,4-dichloro-phenoxy)-phenylcarbamoyl]-vinyl}-indol-1-yl)-acetic acid;

{3-[(E)-2-cyano-2-(2-methoxy-dibenzofuran-3-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(methyl-p-tolyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-(5-chloro-2-methoxy-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-(2-benzyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-3-(11,12-dihydro-6H-dibenzo[b,f]azocin-5-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-(2-benzoyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-3-(2,3-dihydro-indol-1-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(2-phenoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(3,5-dimethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-(3-bromo-4-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(2-methoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-(2-acetyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

[3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-7-methyl-indol-1-yl]-acetic acid.

Preferred novel compounds of the present invention include

{3-[(E)-2-cyano-2-(4-trifluoromethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

(3-{(E)-2-cyano-2-[methyl-((R)-1-phenyl-ethyl)-carbamoyl]-vinyl}-indol-1-yl)-acetic acid;

3-[(E)-3-(1-carboxymethyl-1H-indol-3-yl)-2-cyano-acryloylamino]-benzoic acid methyl ester;

{3-[(E)-2-cyano-2-(9-oxo-9H-fluoren-4-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(4-iodo-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-(3-benzyloxy-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-(benzyl-methyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(2-propyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

[5-bromo-3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;

{3-[(E)-2-cyano-2-(3-methoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(3-nitro-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(3,5-dimethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(9-ethyl-9H-carbazol-3-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(2,3-dihydro-benzo[1,4]dioxin-6-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-(3-chloro-4-methoxy-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

4-[(E)-3-(1-carboxymethyl-1H-indol-3-yl)-2-cyano-acryloylamino]-benzoic acid ethyl ester;

{3-[(E)-2-(4-acetyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(2-isopropyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-(4-tert-butyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(naphthalen-2-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-(benzo[1,3]dioxol-5-ylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-(2-bromo-4-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(4-cyano-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-(4-bromo-3-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

[3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-5-fluoro-indol-1-yl]-acetic acid;

{3-[(E)-2-(biphenyl-4-ylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-isopropyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-chloro-2-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-5-methyl-indol-1-yl]-acetic acid;
{3-[(E)-2-cyano-2-(4-propyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(2,5-dimethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
3-[(E)-3-(1-carboxymethyl-1H-indol-3-yl)-2-cyano-acryloylamino]-4-methyl-benzoic acid methyl ester;
2-[(E)-3-(1-carboxymethyl-1H-indol-3-yl)-2-cyano-acryloylamino]-benzoic acid methyl ester;
{3-[(E)-2-(4-sec-butyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3-iodo-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-bromo-3-chloro-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-cyclohexylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
{3-[(E)-2-cyano-2-(3-fluoro-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-benzyloxy-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3,2'-dimethyl-biphenyl-4-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(5-methoxy-2-methyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
3-{benzyl-[(E)-3-(1-carboxymethyl-1H-indol-3-yl)-2-cyano-acryloyl]-amino}-propionic acid;
{3-[(E)-2-cyano-2-(9-oxo-9H-fluoren-2-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3-ethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(3,5-bis-trifluoromethyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-phenethylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
[3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-6-fluoro-indol-1-yl]-acetic acid;
{3-[(E)-2-(4-bromo-2-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-trifluoromethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-phenoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-cyano-2-(indan-5-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(9H-fluoren-2-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(cyclohexylmethyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-butyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(benzyl-carboxymethyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3-phenoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(9-oxo-9H-fluoren-1-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid.

Other preferred novel compounds of the present invention include
[3-((E)-2-cyano-2-propylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
{3-[(E)-2-cyano-2-(3-methyl-butylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-6-nitro-indol-1-yl]-acetic acid.

The following paragraphs provide definitions of the various chemical moieties that make up the compounds according to the invention and are intended to apply uniformly throughout the specification and claims unless an otherwise expressly set forth definition provides a broader definition.

Therefore, and unless explicitly stated otherwise, the general terms and names used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings:

The term "alkyl" or "lower alkyl", as used herein, alone or in any combination, refers to a saturated aliphatic group including a straight or branched hydrocarbon chain containing 1-8 carbon atoms, preferably 1-4 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, iso-butyl (or 2-methylpropyl), n-pentyl (or n-amyl), iso-pentyl (or iso-amyl), n-hexyl, n-heptyl, n-octyl and the like. The alkyl group can be optionally substituted with one or more substituents, each independently selected from alkenyl, alkoxy, alkoxycarbonyl, alkylcarbonyl, alkylcarbonyloxy, alkylendioxy, alkylsulfinyl, alkylsulfonyl, alkylthio, alkynyl, amino, aminocarbonyl, aryl, arylalkenyl, arylalkyloxy, aryloxy, aryloxycarbonyl, arylsulfinyl, arylsulfonyl, arylthio, carboxy, cyano, formyl,

halogen, haloalkoxy, heterocyclyl, hydroxy, mercapto, nitro, and the like, appended to any carbon atom of the alkyl moiety.

The term "alkenyl"or "lower alkenyl", as used herein, alone or in any combination, refers to a straight or branched hydrocarbon chain containing 2-8 carbon atoms with at least one carbon-carbon double bond ($R_aR_bC=CR_cR_d$). R_a-R_d refer to substituents, each individually and independently selected from hydrogen and alkyl, alkoxy, alkoxyalkyl and the like. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl and the like.

The term "alkoxy" or "lower alkoxy", as used herein, alone or in any combination, refers to an alkyl group appended to the parent molecular moiety through an oxygen bridge. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, hexyloxy, and the like.

The term "aryl", as used herein, alone or in any combination, refers to an carbocyclic group having at least one aromatic ring, e.g. phenyl or biphenyl, or multiple condensed ring systems, in which at least one ring is aromatic, e.g. 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, phenanthryl, fluorenyl, and the like. The aryl group may be optionally substituted with one or more functional groups individually and independently selected from alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonyloxy, alkylendioxy, alkylsulfinyl, alkylsulfinylalkyl, alkylsulfonyl, alkylsulfonylalkyl, alkylthio, alkylthioalkyl, alkynyl, amino, aminoalkyl, aminocarbonyl, aminocarbonylalkyl, aryl, arylalkenyl, arylalkyloxy, arylalkyl, aryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylalkyl, arylthio, arylthioalkyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, formyl, formylalkyl, halogen, haloalkoxy, haloalkyl, heteroaryl, heterocyclyl, hydroxy, hydroxyalkyl, mercapto, nitro, and the like.

The term "arylalkoxy", as used herein, alone or in any combination, refers to an aryl group appended to the parent molecular moiety through an alkoxy group. The aryl group may be unsubstituted or substituted. Representative examples of arylalkoxy include, but are not limited to, 2-phenylethoxy, 5-phenylpentyloxy, 3-naphth-2-ylpropoxy, and the like.

The term "arylalkyl", as used herein, alone or in any combination, refers to an aryl group appended to the parent molecular moiety through an alkyl group. The aryl group may be unsubstituted or substituted. Representative examples of arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, 2-naphth-2-ylethyl, and the like.

The term "aryloxy", as used herein, alone or in any combination, refers to an aryl group appended to the parent molecular moiety through an oxygen bridge. The aryl group can be unsubstituted or substituted. Representative examples of aryloxy include, but are not limited to, phenoxy, naphthyloxy, 3-bromophenoxy, 4-chlorophenoxy, 4-methylphenoxy, 3,4-dimethoxyphenoxy, and the like.

The term "arylcarbonyl" or "aroyl", as used herein, alone or in any combination, refers to an aryl group appended to the parent molecular moiety through a carbonyl group. Representative examples of alkylcarbonyl include, but are not limited to, phenylcarbonyl (or benzoyl), naphthylcarbonyl and the like.

The term "carbamoyl", as used herein, alone or in any combination, refers to a -$C(O)NR_eR_f$ group. R_e and R_f are substituents, each individually and independently selected from hydrogen, alkyl, arylalkyl, and the like.

The term "carbonyl", as used herein, alone or in any combination, refers to a -C(O) group.

The term "carboxy", as used herein, alone or in any combination, refers to a -CO_2H group.

The term "carboxyalkyl", as used herein, alone or in any combination, refers to a carboxy group appended to the parent molecular moiety through an alkyl group. Representative examples of carboxyalkyl include, but are not limited to, carboxymethyl, 2-carboxyethyl, 3-carboxypropyl, and the like.

The term "cyano", as used herein, alone or in any combination, refers to a -C≡N group.

The term "cycloalkyl", as used herein, alone or in any combination, refers to a saturated cyclic hydrocarbon moiety containing 3-15 carbon atoms, optionally substituted with one or more groups, each individually and independently selected from alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonyloxy, alkylendioxy, alkylsulfinyl, alkylsulfinylalkyl, alkylsulfonyl, alkylsulfonylalkyl, alkylthio, alkylthioalkyl, alkynyl, amino, aminoalkyl, aminocarbonyl, aminocarbonylalkyl, aryl, arylalkenyl, arylalkyloxy, arylalkyl, aryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylalkyl, arylthio, arylthioalkyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, formyl, formylalkyl, halogen, haloalkoxy, haloalkyl, heterocyclyl, hydroxy, hydroxyalkyl, mercapto, nitro, and the like. Representative examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like. In polycyclic cycloalkyl groups one of the distal rings may be aromatic, e.g., 1-indanyl, 2-indanyl, tetrahydronaphthalene, and the like.

The term "cyclylalkyl", as used herein, alone or in any combination, refers to an cycloalkyl group appended to the parent molecular moiety through an alkyl group. Representative examples of cyclylalkyl include, but are not limited to, cyclopropylmethyl, cyclohexylethyl, and the like.

The term "formyl", as used herein, alone or in any combination, refers to a -C(O)H group.

The term "halo" or "halogen", as used herein, alone or in any combination, refers to fluorine, bromine, chlorine, and iodine.

The term "heterocyclyl", as used herein, alone or in any combination, refers to a monocyclic, bicyclic or polycyclic ring system containing up to 15 ring atoms, at least one of these being a hetero atom independently selected from nitrogen, oxygen or sulfur. The ring system may be saturated, partially unsaturated, unsaturated or aromatic. Representative examples of heterocyclyl include, but are not limited to, furyl, imidazolyl, imidazolinyl, imidazolidinyl, isothiazolyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolyl, oxazolinyl, oxazolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrrolyl, pyrrrolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrofuranyl, tetrahydrothienyl, thiadiazolyl, thiazolyl, thiazolinyl, thiazolidinyl, thienyl, thiomorpholinyl, 1,1-dioxothiomorpholinyl, benzimidazolyl, benzothiazolyl, benzothienyl, benzoxazolyl, benzofuranyl, indolyl, indolinyl, isobenzofuranyl, isobenzothienyl, isoindolyl, isoindolinyl, isoquinolinyl, quinolinyl, and the like. Defined heterocyclyl moieties may be optionally substituted with one or more groups, each individually and independently selected from alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonyloxy, alkylendioxy, alkylsulfinyl, alkylsulfinylalkyl, alkylsulfonyl, alkylsulfonylalkyl, alkylthio, alkylthioalkyl, alkynyl, amino, aminoalkyl, aminocarbonyl, aminocarbonylalkyl, aryl, arylalkenyl, arylalkyloxy, arylalkyl, aryloxy, aryloxycarbonyl, aryloxycarbonylalkyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylalkyl, arylthio, arylthioalkyl, carboxy, carboxyalkyl, cyano, cyanoalkyl, cycloalkyl, formyl, formylalkyl, halogen, haloalkoxy, haloalkyl, heterocyclyl, heteroaryl, hydroxy, hydroxyalkyl, mercapto, nitro, and the like.

The term "heteroaryl", as used herein, alone or in any combination, is a special case of heterocyclyl and refers to a mono- or bicyclic or polycyclic aromatic ring system, in which at least one heterocyclic ring is aromatic.

The term "nitro", as used herein, alone or in any combination, refers to a $-NO_2$ group.

The term "oxo", as used herein, alone or in any combination, refers to a =O group.

The term "oxy", as used herein, alone or in any combination, refers to a -O- group.

Within the scope of the present invention, unless indicated otherwise, compounds of Formula I or or the novel compounds of the Formula II and pharmaceutically acceptable salts thereof are included that may exist in, and be isolated in, isomeric forms, including cis- or trans isomers or mixtures thereof, and tautomers. Other compounds of this invention may contain one or more stereogenic or asymmetric centers, such as one or more asymmetric carbon atoms, and thus may give rise to optically pure enantiomers, mixtures of enantiomers, racemates, enantiomer-pure diastereomers, mixtures of diastereomers, epimers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)-, (S)- or (R,S)-configured, preferably in the (R)- or (S)-configuration. Such isomers can be obtained by methods within the knowledge of one skilled in the art, e.g. by stereochemically controlled synthesis using chiral synthons or chiral reagents, or by means of classical separation techniques, such as chromatographic or crystallization methods, or by other methods known in the art, such as through formation of diastereomeric salts, for example by salt formation with an enantiomerically pure chiral acid, or by means of chromatography, for example by using chromatographic materials modified with chiral ligands. Furthermore, the present invention refers to compounds containing centers of any geometric asymmetry, like, for example, unsymmetrically substituted olefinic double bond, including E or Z geometric isomers and mixtures thereof. Generally, pure isomers of compounds of Formula I or II are preferred over isomeric mixtures.

In the present invention, the compounds of Formula I or II may be used in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salts" refers to relatively nontoxic, inorganic or organic acid and base addition salts, which retain the biological effectiveness and properties of the parent compound, and which are not

biologically or otherwise undesirable (see, e.g., Berge et al., J. Pharm. Sci. 1977, 66, 1-19).

Certain compounds of the present invention can contain one or more basic functional groups, such as amino, alkylamino, or arylamino, and, thus, be capable of forming pharmaceutically acceptable acid addition salts. These acid addition salts may be prepared by standard procedures in a suitable solvent from the parent compound of Formula I or II, with an appropriate amount of an inorganic acid, including, but not limited to, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, or phosphoric acid; or of an organic acid, including, but not limited to, acetic acid, propionic acid, octanoic acid, decanoic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, ascorbic acid, amino acids, such as glutamic acid or aspartic acid, benzoic acid, cinnamic acid, salicylic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, or other acidic organic compounds.

Certain compounds of the present invention may, on the other hand, contain one or more acidic functional groups and, thus, be capable of forming pharmaceutically acceptable base addition salts. These salts can be prepared by addition of an appropriate amount, usually in stoichiometric ratio, of an alkaline reagent, such as hydroxide, carbonate or alkoxide, containing the appropriate cation, to the free acid in a suitable solvent. Preferred inorganic salts include, but are not limited to, ammonium, sodium, potassium, calcium or magnesium, also zinc salts and the like. Preferred salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines, cyclic amines, and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, lysine, arginine, N-ethylpiperidine, piperidine, polyamine resins, and the like.

Compounds of the present invention containing both acidic and basic groups can also form internal salts (zwitter ions).

For isolation or purification purposes, it is also possible to use pharmaceutically unacceptable salts, for example perchlorates, picolinates, picrates, or the like. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed, where applicable in the form of pharmaceutical preparations, and these are therefore preferred.

Certain compounds of Formula I or II, including their salts, may exist in solvated as well unsolvated forms, such as, for example, hydrated forms, or their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present. The present invention encompasses all such solvated and unsolvated forms.

The present invention also relates to prodrug derivatives of the parent compounds of Formula I or II. The term "prodrug" refers to pharmacologically inactive precursors of a drug that may be converted into its therapeutically active form under physiological conditions *in vivo*, for example, when they undergo solvolysis, or enzymatic degradation in blood, or in cells, (Bundgard H., "Design of Prodrugs", pp. 7-9, 21-24, Elsevier, Amsterdam (1985); Silverman R. B., "The Organic Chemistry of Drug Design and Drug Action", pp. 352-401, Academic Press, San Diego, CA (1992); Higuchi T. et al., "Pro-drug as Novel Delivery Systems", A.C.S. Symposium Series, Vol. 14). The term "prodrug" also includes any covalently bonded carriers, which release the active parent compound *in vivo* when administered to a mammal. Prodrug modifications of a compound often offer advantages of solubility, bioavailability, absorption, tissue compatibility, tissue distribution, or delayed release in the mammalian organism. Prodrugs are variations or derivatives of the compounds of Formula I, which have groups cleavable under metabolic conditions, for example, pharmaceutically acceptable esters, or amides. Such groups can be cleaved enzymatically or non-enzymatically, or hydrolytically to the free hydroxy, carboxy, or amino group of the active parent compound. In another embodiment, the prodrug is a reduced form, which is oxidized *in vivo* to the therapeutic compound, for example, a thiol, which is oxidized to a sulfonate or sulfate, an alcohol to a carboxylic acid.

Further included within the scope of the present invention are pharmaceutically acceptable esters of the compounds of Formula I, II, III or IV. The term "pharmaceutically acceptable esters" refers to relatively non-toxic, esterified products of the parent compound. These esters can be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compounds in its free acid or hydroxyl form with a suitable esterifying agent. Carboxylic acids can be converted into esters *via* treatment with an alcohol in the presence of a catalyst. Hydroxyl containing derivatives can be converted into esters *via* treatment with an esterifying agent such as alkanoyl halides. The term further includes lower hydrocarbon groups capable of being solvated under physiological conditions, for example, alkyl esters, preferred methyl, ethyl, and propyl ester, methoxymethyl ester, methylthiomethyl ester, pivaloyloxymethyl ester and the like (see, e.g., Berge et al., J. Pharm. Sci. 1977, 66, 1-19).

The compounds of the present invention have useful, in particular pharmacologically useful, properties. They are able to specifically antagonize the effect of endogenous PGD_2 on the CRTH2 receptor.

A compound or a pharmaceutical composition of the invention may be used as a drug (medicine) or therapeutic agent for prevention and/ or treatment of both chronic and acute allergic/immune disorders such as allergic asthma, rhinitis, chronic obstructive pulmonary disease (COPD), dermatitis, inflammatory bowel disease, rheumatoid arthritis, allergic nephritis, conjunctivitis, atopic dermatitis, bronchial asthma, food allergy, systemic mast cell disorders, anaphylactic shock, urticaria, eczema, itching, inflammation, ischemia-reperfusion injury, cerebrovascular disorders, pleuritis, ulcerative colitis, eosinophil-related diseases, such as Churg-Strauss syndrome and sinusitis, basophil-related diseases, such as basophilic leukemia and basophilic leukocytosis.

In another aspect, the compounds of Formula I may be used as standard or reference compounds in tests or assays involving the inhibition of the CRTH2 receptor. Such compounds could be made commercially available for use as a reference, quality standard or control, for example in pharmaceutical research when developing new assays or protocols related to CRTH2 activity.

As mentioned earlier, compounds of Formula I, or salts, or prodrugs thereof, antagonize the PGD_2 activation of the CRTH2 receptor. The biological effect of such compounds may be tested in a variety of *in vitro*, *ex vivo* and *in vivo* assays.

The ability of the compounds of Formula I to bind to the CRTH2 receptor may be measured by methods similar to those described in Sawyer N. et al., *Br. J. Pharmacol.*, 2002, 137, 1163-1172 and by the method described below in Example B-1.

With this type of assay, IC_{50} values (i.e. the concentrations where half-maximal inhibition of the interaction is found) in the range of 0.001 to 10 μM, preferably values below 1 μM, in particular values below 0.05 μM, are found with test compounds of Formula I.

A functional assay with cells expressing the human CRTH2 receptor may be used to detect changes in the levels of intracellular calcium concentration following compound treatment. After addition of the compound the cells are challenged with PGD_2. In a Fluorescent Imaging Plate Reader (FLIPR™, Molecular Devices, Sunnyvale, California) fluorescence emission is recorded during both additions, emission peak values above base level after PGD_2 addition were exported, normalized to low controls (no PGD_2) and high controls (no active compound). The relative values of the remaining activity were used to determine IC_{50} values by curve fitting the data to a single site to a four-parameter logistic sigmoid dose response curve of the equation (A+((B-A)/(1+((C/x)^D)))).

The ability of the compounds to antagonize PGD_2 induced change of intracellular calcium levels *via* CRTH2 activation may be measured by methods known of one skilled in the art or by the method described below in Example B-2.

With this assay, IC_{50} values (i.e. the concentration of a compound at which the remaining activity is 50%) in the range of 0.001 and 10 μM, preferably below 0.5 μM, are obtained with test compounds of Formula I.

The results of these assays clearly demonstrate, that the present invention provides functional antagonists of the PGD_2 receptor.

On the basis of the biological studies discussed hereinabove, a compound of Formula I according to the invention may show therapeutic efficacy against chronic and acute allergic/immune disorders such as allergic asthma, rhinitis, chronic obstructive pulmonary disease (COPD), dermatitis, inflammatory bowel disease, rheumatoid arthritis, allergic nephritis, conjunctivitis, atopic dermatitis, bronchial asthma, food allergy, systemic mast cell disorders, anaphylactic shock, urticaria, eczema, itching, inflammation, ischemia-reperfusion injury, cerebrovascular disorders, pleuritis, ulcerative colitis, eosinophil-related diseases, such as Churg-Strauss syndrome and sinusitis, basophil-related diseases, such as basophilic leukemia and basophilic leukocytosis.

A compound of Formula I, a pharmaceutically acceptable salt or a prodrug thereof, can be administered alone in pure form or in combination with one or more other therapeutic agents, possible combination therapy taking the form of fixed combinations or the administration of a compound of the invention and one or more other therapeutic agents being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic agents. A compound of Formula I can besides or in addition be administered especially for prevention and/or treatment of both chronic and acute allergic or immune disorders in combination with other inflammatory diseases. Long- term therapy is equally possible as is adjuvant

therapy in the context of other treatment strategies, as described above. Other possible treatments are preventive therapies, for example in patients at risk.

The invention relates to pharmaceutical compositions comprising compounds of Formula I, to their use in therapeutic, in a broader aspect of the invention also prophylactic treatment or a method of treatment of the diseases mentioned above, to the compounds for said use and to the preparation of pharmaceutical formulations (medicines).

The pharmaceutically acceptable compounds of the present invention may be used, for example, for the preparation of pharmaceutical compositions that comprise an effective amount of the active ingredient together or in admixture with a significant amount of one or more inorganic, organic, solid or liquid, pharmaceutically acceptable carriers.

The invention relates also to a pharmaceutical composition that is suitable for administration to a warm-blooded animal, especially a human (or to cells or cell lines derived from a warm-blooded animal, especially a human, for the treatment or, in a broader aspect of the invention, prevention of (i.e. prophylaxis against) a disease that responds to blockade of the interaction of the CRTH2 receptor with PGD_2, comprising an amount of a compound of Formula I or a pharmaceutically acceptable salt or a prodrug thereof, which is effective for said inhibition, together with at least one pharmaceutically acceptable carrier.

The pharmaceutical compositions according to the invention are those for enteral administration, such as nasal, buccal, rectal, dermal or, especially oral administration, and for parenteral administration, such as intramuscular, intravenous or subcutaneous, intrasternal, intravitreal, injection or infusion, to warm-blooded animals, especially humans. Such compositions comprise an effective dose of the pharmaceutically active ingredient, alone or together with a significant amount of a pharmaceutically acceptable carrier. The dosage of the active ingredient depends on the species of warm-blooded

animal, the body weight, the age and the individual conditions, individual pharmacokinetic data, the disease to be treated and the mode of administration.

The invention relates also to a process or a method for the treatment of a pathological condition mentioned hereinabove, especially a disease, which responds to blockade of the interaction of the CRTH2 receptor with PGD_2, especially allergic/immune disorders such as allergic asthma, rhinitis, chronic obstructive pulmonary disease (COPD), dermatitis, inflammatory bowel disease, rheumatoid arthritis, allergic nephritis, conjunctivitis, atopic dermatitis, bronchial asthma, food allergy, systemic mast cell disorders, anaphylactic shock, urticaria, eczema, itching, inflammation, ischemia-reperfusion injury, cerebrovascular disorders, pleuritis, ulcerative colitis, eosinophil-related diseases, such as Churg-Strauss syndrome and sinusitis, basophil-related diseases, such as basophilic leukemia and basophilic leukocytosis. The compounds of Formulae I or salts or prodrugs thereof can be administered as such or especially in the form of pharmaceutical compositions.

The dose to be administered to warm-blooded animals, for example humans of approximatively 70 kg body weight, is preferably from approximatively 3 mg to approximatively 30 g, more preferably from approximatively 10 mg to approximatively 1000 mg per person per day, divided preferably into 1 to 3 single doses which may, for example, be of the same size. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, the weight, and response of the individual patient, the severity of the patient's symptoms, and the like, for example, children usually receive half of the adults dose.

The pharmaceutical compositions comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient. Pharmaceutical compositions according to the invention may be, for example, in unit dosage forms such as coated and uncoated tablets, pills, ampoules, vials, suppositories,

dragées, or capsules. Further dosage forms are, for example, ointments, creams, pastes, emulsions, foams, chewable gums, tinctures, lip-sticks, drops, sprays or aerosols, syrups or elixirs, dispersions, transdermal patches or pads, or *via* an intravitreal device that releases the compound in a sustained capacity, and the like. Examples are capsules containing from about 0.05 g to about 1.0 g active ingredient.

The pharmaceutical compositions of the present invention are prepared in a manner known, *per se*, for example by means of conventional mixing, granulating, coating, dissolving, lyophilizing or confectioning processes.

Solutions of the active ingredient, and also suspensions, and especially isotonic aqueous solutions or suspensions, are preferably used, it being possible, for example in the case of lyophilized compositions, that comprise the active ingredient alone or together with a carrier, for example mannitol, for such solutions or suspensions to be produced prior to use. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers and are prepared in a manner known *per se*, for example by means of conventional dissolving or lyophilizing processes. The said solutions or suspensions may comprise viscosity-increasing substances, such as sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone or gelatin.

Suspensions in oil comprise as the oil component the vegetable, synthetic or semi-synthetic oils customary for injection purposes. There may be mentioned as such especially liquid fatty acid esters that contain as the acid component a long-chain fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms, for example lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brasidic acid or linoleic acid, if desired with the addition of antioxidants, for example vitamin E, β-carotene or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of those fatty acid esters has a maximum of 6

carbon atoms and is mono- or poly-hydroxy, for example a mono-, di- or trihydroxy, alcohol, for example methanol, ethanol, propanol, butanol, or pentanol or the isomers thereof, but especially glycol and glycerol. The following examples of fatty acid esters are therefore to be mentioned: ethyl oleate, isopropyl myristate, isopropyl palmitate, "Labrafil M2375" (polyoxyethylene glycerol trioleate, Gattefossé, Paris), "Miglyol 812" (triglyceride of saturated fatty acids with chain length of C8 to C12, Hüls AG, Germany), but especially vegetable oils, such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and more especially groundnut oil.

The injection or infusion compositions are prepared in customary manner under sterile conditions; the same applies also to introducing the compositions into ampoules or vials and sealing the containers.

Pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, if desired granulating a resulting mixture, and processing the mixture, if desired or necessary, after the addition of appropriate excipients, into tablets, dragée cores or capsules. It is also possible for them to be incorporated into plastics carriers that allow the active ingredients to diffuse or be released in measured amounts.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and binders, such as starch pastes using for example corn, wheat, rice, or potato starch, gelatin, tragacanth, methylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, and/or carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable, optionally enteric, coatings, there being used, inter alia,

concentrated sugar solutions which may comprise gum Arabic, talc, polyvinylpyrrolidone, polyethylene glycol, and/or titanium dioxide, or coating solutions in suitable organic solvents, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as ethylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Capsules are dry-filled capsules made of gelatin and of soft sealed capsules made of gelatine and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may comprise the active ingredient in the form of granules, for example with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and if desired with stabilizers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable oil excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols, it being possible also for stabilizers and/or antibacterial agents to be added. Dyes or pigments may be added to the tablets or dragée coatings or the capsule casings, for example for identification purposes or to indicate different doses of active ingredient.

For parenteral administration, aqueous solutions of an active ingredient in water-soluble form, for example of a water-soluble salt, or aqueous injection suspensions that contain viscosity- increasing substances and stabilizers, are especially suitable. The active ingredient, optionally together with excipients, can also be in the form of a lyophilizate and be made into a solution before parenteral administration by the addition of solvents. A further object of the invention is a process for preparing pyridoindol derivatives according to Formula I. Compounds according to Formula I of the present invention are prepared according to the general sequence of reactions outlined in the schemes below, wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in Formula I. The compounds obtained may also be converted into a pharmaceutically acceptable salt thereof in a manner known *per se*.

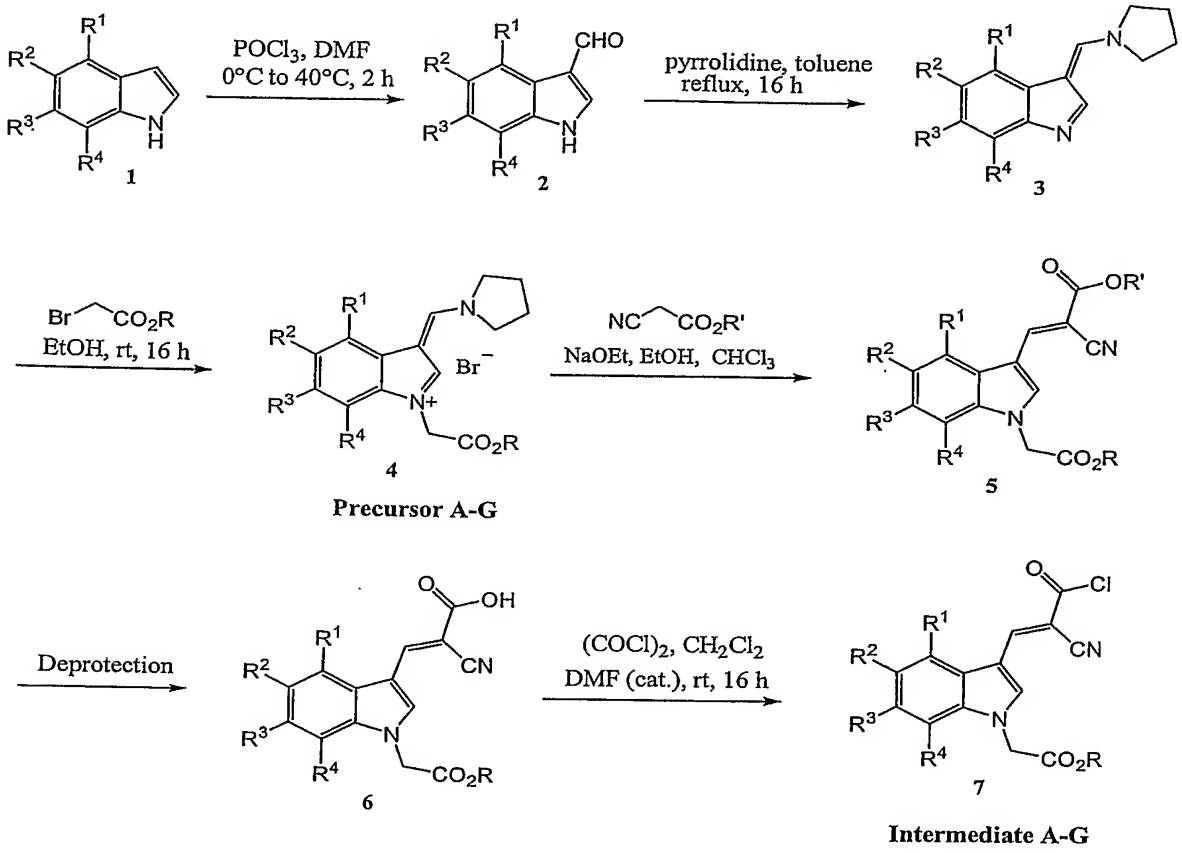
Compounds of the invention may be manufactured by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by Larock R. C. in "Comprehensive organic transformations: a guide to functional group preparations", VCH publishers, 1999.

In the reactions described hereinafter, it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for example see Greene T. W. and Wuts P. G. M. in "Protective groups in organic synthesis" Wiley-Interscience, 1999.

Generally, the synthesis of indolacetic acid derivatives of Formula (I) starts as outlined in Scheme 1 and 2 with indole of Formula **1**, which by means of phosphorous oxychloride in dimethylformamide is converted in a Vilsmeyer reaction to the formyl derivative of Formula **2** (R. Gastpar et al., *J. Med. Chem.* 1998, *41*, 4965-4972). Subsequent condensation with a secondary amine, such as pyrrolidine or the like, in a solvent appropriate to azeotropically remove water formed in a reaction, such as toluene, benzene or the like, leads to Schiff base of Formula **3**, that then reacts with a compound of Formula L-CH_2CO_2R, in which R represents an alkyl group, preferably ethyl or tert.-butyl, and L is a leaving group, in the presence of a base, such as caesium carbonate, sodium hydride or the like, in a suitable solvent, such as alcohol, preferably ethanol, or acetone, tetrahydrofuran, dioxane, to yield indolium salt of Formula **4**. Suitable L is a leaving group such as halo, in particular bromo or chloro. Preferably, the compound of Formula L-CH_2CO_2R is ethyl bromoacetate.

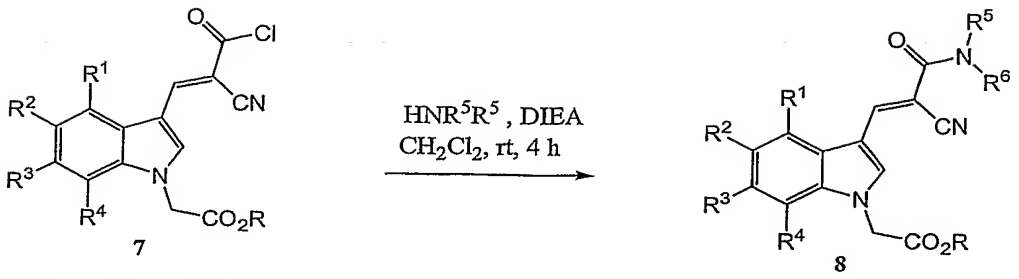
Indolium salt of Formula **4** is condensed with cyanoacetic acid ester of Formula NC-CH_2-COOR', wherein R' represents an alkyl group, preferably ethyl or tert.-butyl, in the presence of a base, such as sodium ethoxide, to form cyanoacrylic ester of Formula **5** (T. Moriya et al., *Chem. Pharm. Bull.* 1980, *28*, 1711-1721). Cleavage of the ester group, either under acidic or basic conditions, such as TFA in dichloromethane or sodium hydroxide in THF, respectively, gave carboxylic acid of Formula **6**, which then was converted to the corresponding acyl halide of Formula **7** by means of a halogenating reagent under conditions known to a skilled person. Preferably, the carboxylic acid is converted to the acid chloride using oxalyl chloride in the presence of a catalytical

amount of dimethylformamide in an appropriate solvent, such as dichloromethane or toluene or the like.



Scheme 1

Step a)

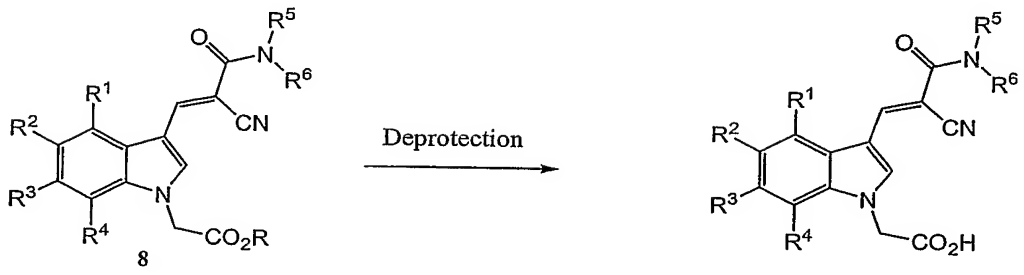


7

8

Intermediate A-G

Step b)



8

(I,4)

Scheme 2

The treatment of an acyl halide of Formula **7** with a primary amine of Formula R^6-NH_2 in a suitable solvent, such as dichloromethane, tetrahydrofuran, or N,N-dimethylformamide, gives a N-substituted amide of Formula **8**, wherein R^5 is a hydrogen atom, while a secondary amine of Formula NHR^5R^6 gives a N,N-disubstituted amide of Formula **8**. Preferably a base such as triethylamine, N,N-diisopropylethylamine, N-ethyl-morpholine, N-methylpiperidine, or pyridine is added to combine with the liberated hydrochloric acid.

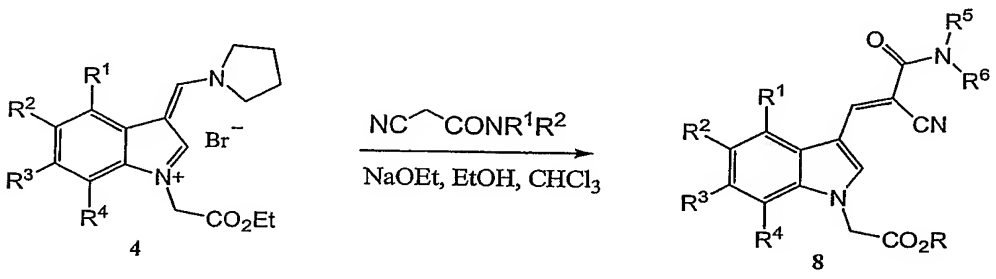
Hydrolysis of the ester group R in Formula **8** can be carried out using routine procedures, as outlined in Scheme 2, Step b), for example by stirring with aqueous sodium hydroxide, or trifluoroacetic acid to give a compound of Formula (I.,4).

Alternatively, indolacetic acid derivatives of Formula I can be synthesized in two consecutive steps as outlined in Scheme 3, starting from abovementioned Schiff base of

Formula **4** (Step c), which is reacted first with 2-cyano-acetamide of Formula NC-CH_2-$CONR^5R^6$ to form an amide of Formula **8**. Final deprotection under standard conditions, as outlined in Scheme 3, Step b), delivers a final compound of Formula (I,4).

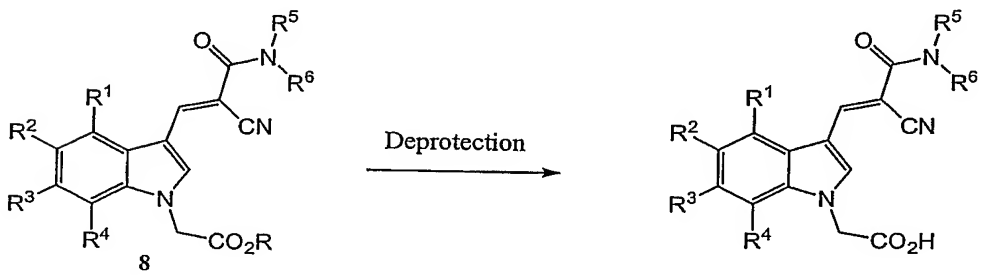
The reagent 2-cyano-acetamide of Formula NC-CH_2-$CONR^5R^6$ is prepared from cyanoacetic acid and a primary or secondary amine under conditions known to a skilled person.

Step c)



4 **Precursor A-G** 8

Step b)



8 (I,4)

Scheme 3

Particular embodiments of the invention are described in the following Examples, which serve to illustrate the invention in more detail without limiting its scope in any way.

Examples

Temperatures are indicated in degrees Celsius (°C). Unless otherwise indicated, the reactions take place at room temperature (rt).

In mixtures, relations of parts of solvent or eluent or reagent mixtures in liquid form are given as volume relations (v/v), unless indicated otherwise.

Abbreviations and acronyms used:

AcOH: acetic acid, NH_4OH: ammonium hydroxide, BSA: bovine serum albumin, CH_2Cl_2: dichloromethane, DIEA: N,N-diisopropylethylamine, DMF: N,N-dimethylformamide, DMSO: dimethyl sulfoxide, EDTA: ethylenediaminetetraacetic acid, Et_3N: triethylamine, EtOAc: ethyl acetate, EtOH: ethanol, g: gram, h: hour, H_2O: water, HCl: hydrochloric acid, HEPES: 4-(2-hydroxyethyl)-piperazin-1-ethanesulfonic acid buffer, HPLC: high-performance liquid chromatography, k: kilo, K_2CO_3: potassium carbonate, $KHSO_4$: potassium hydrogensulfate, l: liter, $MgCl_2$: magnesium chloride, $MgSO_4$: magnesium sulfate, µ: micro, m: milli, mol: mole, M: molar, MeOH: methanol, Me: methyl, min: minute, ESI-MS: electrospray ionization mass spectrometry, N: normality of solution, NaN_3: sodium azide, NaCl: sodium chloride, $NaHCO_3$: sodium hydrogencarbonate, Na_2CO_3: sodium carbonate, NaOH: sodium hydroxide, Na_2SO_4: sodium sulfate, PBS: phosphate buffer saline, PGD_2: prostaglandin D2, PMSF: phenyl methanesulfonyl fluoride, $POCl_3$: phosphorous oxychloride, THF: tetrahydrofuran, t_R: retention time, Tris: tris-(hydroxymethyl)aminomethane buffer.

Analytical HPLC conditions as used in the Examples below:

LC-1: Analytical HPLC on a Xterra™ MS C_{18} column (50 x 2.1 mm, 5µm, Waters): Linear gradient of water/ 0.06% formic acid (A) and acetonitrile/ 0.06% formic acid (B) from 5% to 95% B over 6 min; flow rate 0.25 ml/min, detection at 215 nm.

LC-2: Analytical HPLC on a GromSil MS C_{18} column (50 x 2.1 mm, 5µm, Waters): Linear gradient of water/ 0.06% formic acid (A) and acetonitrile/ 0.06% formic acid (B) from 5% to 95% B over 6 min; flow rate 0.25 ml/min, detection at 215 nm.

Synthesis of Precursor A-G of Formula 4

Precursor A

1-Ethoxycarbonylmethyl-3-pyrrolidin-1-ylmethylene-3H-indolium bromide

A-a) 3-Pyrrolidin-1-yl-methylene-3H-indole:

In a round bottom flask equipped with a Dean-Starck condenser, 1H-indole-3-carbaldehyde (40 g, 0.275 mmol) and pyrrolidine (27 ml, 0.330 mmol) were suspended in toluene (480 ml) and kept heating at reflux overnight. After cooling to rt, the solid was filtered off, washed with toluene and recrystallized from THF (100 ml) affording subtitle compound (47.7 g) as a reddish solid in 87% yield: t_R (LC-2) 0.47 min; ESI-MS(+): *m/z* 199.46 $[M+H]^+$ (calcd 198.26 for $C_{13}H_{14}N_2$).

A-b) 1-Ethoxycarbonylmethyl-3-pyrrolidin-1-ylmethylene-3H-indolium bromide:

Ethyl bromoacetate (6.1 ml, 55.4 mmol) was added dropwise to a stirred solution of 3-pyrrolidin-1-yl-methylene-3H-indole (10 g, 50.4 mmol) in EtOH (40 ml) and the reaction mixture was kept stirring at rt overnight. The solid was filtered off, washed with small portions of EtOH and then dried in vacuo, affording title compound (17 g) as a beige solid in 93% yield: t_R (LC-1) 1.45 min; ESI-MS(+): *m/z* 285.31 $[M]^+$ (calcd 365.26 for $C_{17}H_{21}BrN_2O_2$).

Precursor B

5-Bromo-1-ethoxycarbonylmethyl-3-pyrrolidin-1-ylmethylene-3H-indolium bromide

The title compound is prepared using a procedure analogous to Precursor A, substituting 5-bromo-1H-indole-3-carbaldehyde for 1H-indole-3-carbaldehyde.

Preparation of 5-bromo-1H-indole-3-carbaldehyde:

Dry DMF (7.5 ml) is cooled to 0°C and treated dropwise with $POCl_3$ (3.66 ml, 40 mmol). After stirring at this temperature for 15 min, a solution of 5-bromo-1H-indole (784 mg, 4 mmol) in dry DMF (2 ml) is added and the reaction mixture is allowed to warm to rt within 1 h. Stirring is continued at 40°C for an additional hour, then the reaction mixture is cooled to rt and poured onto ice. Aqueous NaOH solution is added to neutralize the acidic solution, adjusting to pH 6. After stirring overnight at rt, the

precipitate was collected by filtration, washed with water and dried under high vacuum to give pure subtitle compound (932 mg) as a beige solid in quantitative yield: t_R (LC-2) 1.85 min; ESI-MS(+): *m/z* 226.10 $[M+2]^+$ (calcd 224.05 for C_9H_6BrNO).

Precursor C

1-Ethoxycarbonylmethyl-7-methyl-3-pyrrolidin-1-ylmethylene-3H-indolium bromide

The title compound is prepared using a procedure analogous to Precursor B, substituting 7-methyl-1H-indole-3-carbaldehyde for 5-bromo-1H-indole-3-carbaldehyde.

Preparation of 7-methyl-1H-indole-3-carbaldehyde is performed analogous to 5-bromo-1H-indole-3-carbaldehyde.

Precursor D

1-Ethoxycarbonylmethyl-5-fluoro-3-pyrrolidin-1-ylmethylene-3H-indolium; bromide

The title compound is prepared using a procedure analogous to Precursor B, substituting 5-fluoro-1H-indole-3-carbaldehyde for 5-bromo-1H-indole-3-carbaldehyde.

Preparation of 5-fluoro-1H-indole-3-carbaldehyde is performed analogous to 5-bromo-1H-indole-3-carbaldehyde.

Precursor E

1-Ethoxycarbonylmethyl-5-methyl-3-pyrrolidin-1-ylmethylene-3H-indolium bromide

The title compound is prepared using a procedure analogous to Precursor A, substituting 5-methyl-1H-indole-3-carbaldehyde for 1H-indole-3-carbaldehyde.

Preparation of 5-methyl-1H-indole-3-carbaldehyde is performed analogous to 5-bromo-1H-indole-3-carbaldehyde.

Precursor F

1-Ethoxycarbonylmethyl-6-fluoro-3-pyrrolidin-1-ylmethylene-3H-indolium bromide

The title compound is prepared using a procedure analogous to Precursor A, substituting Precursor F for Precursor A.

Preparation of 6-fluoro-1H-indole-3-carbaldehyde is performed analogous to 5-bromo-1H-indole-3-carbaldehyde.

Precursor G

1-Ethoxycarbonylmethyl-6-nitro-3-pyrrolidin-1-ylmethylene-3H-indolium bromide

The title compound is prepared using a procedure analogous to Precursor A, substituting Precursor G for Precursor A.

Preparation of 6-nitro-1H-indole-3-carbaldehyde is performed analogous to 5-bromo-1H-indole-3-carbaldehyde.

Preparation of Intermediate A-G of Formula 7:

Intermediate A

Ethyl [3-(2-chlorocarbonyl-2-cyano-vinyl)-indol-1-yl]-acetetate

To a stirred suspension of 2-cyano-3-(1-ethoxycarbonylmethyl-1H-indol-3-yl)-acrylic acid (3.0 g, 10 mmol) in dry dichloromethane(120 ml), in the presence of a few drops of dry DMF, was added oxalyl chloride (1.7 ml, 20 mmol). After stirring at rt overnight, the volatiles were removed under reduced pressure, the residue azeotoped twice with dry toluene and dried in vacuo, affording crude title compound (3.18 g) in quantitative yield. This material was stored under argon and was used without further purification.

A-c) 2-Cyano-3-(1-ethoxycarbonylmethyl-1H-indol-3-yl)-acrylic acid

To a stirred solution of Precursor A (1-ethoxycarbonylmethyl-3-pyrrolidin-1-yl-methylene-3H-indolium bromide, 4.0 g, 10.8 mmol) and tert-butyl cyanoacetate (15.0g, 10.8 mmol) in chloroform (100 ml) was added dropwise a solution of sodium ethylate (0.74 g, 10.8 mmol) in dry EtOH (40 ml). The reaction mixture was kept stirring at rt overnight, then diluted with EtOAc (60 ml) and water (30 ml), acidified to pH 3 by adding 1N aqueous HCl. After phase separation, the aqueous phase was extracted twice

with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and the solvent removed under reduced pressure. The residue was dissolved in dichloromethane (20 ml) and treated with trifluoroacetic acid (8.3 ml, 108 mmol) at rt for 4 h. The volatiles were removed under reduced pressure and the residue was azeotoped three times with toluene, then re-crystallized from EtOAc affording subtitle compound (3.15 g) as a yellow solid in 97% yield: t_R (LC-2) 1.98 min; ESI-MS(+): *m/z* 324.35 $[M+Na]^+$ (calcd 298.29 for $C_{16}H_{14}N_2O_4$).

Intermediate B

Ethyl [3-(2-chlorocarbonyl-2-cyano-vinyl)-5-bromo-indol-1-yl]-acetate

The title compound is prepared using a procedure analogous to Intermediate A, substituting Precursor B (5-bromo-1-ethoxycarbonylmethyl-3-pyrrolidin-1-ylmethylene-3H-indolium) for Precursor A.

Intermediate C

Ethyl [3-(2-chlorocarbonyl-2-cyano-vinyl)-7-methyl-indol-1-yl]-acetate

The title compound is prepared using a procedure analogous to Intermediate A, substituting Precursor C for Precursor A.

Intermediate D

Ethyl [3-(2-chlorocarbonyl-2-cyano-vinyl)-5-fluoro-indol-1-yl]-acetate

The title compound is prepared using a procedure analogous to Intermediate A, substituting Precursor D for Precursor A.

Intermediate E

Ethyl [3-(2-chlorocarbonyl-2-cyano-vinyl)-5-methyl-indol-1-yl]-acetate

The title compound is prepared using a procedure analogous to Intermediate A, substituting Precursor E for Precursor A.

Intermediate F

Ethyl [3-(2-chlorocarbonyl-2-cyano-vinyl)-6-fluoro-indol-1-yl]-acetate

The title compound is prepared using a procedure analogous to Intermediate A, substituting Precursor F for Precursor A.

Intermediate G

Ethyl [3-(2-chlorocarbonyl-2-cyano-vinyl)-6-nitro-indol-1-yl]-acetate

The title compound is prepared using a procedure analogous to Intermediate A, substituting Precursor G for Precursor A.

Example 1

[3-((E)-2-Cyano-2-phenylcarbamoyl-vinyl)-indol-1-yl]-acetic acid

Step A) Ethyl [3-(2-cyano-2-phenylcarbamoyl-vinyl)-indol-1-yl]-acetate:
Aniline (8 µl, 0.09 mmol) is added to a stirred solution of ethyl [3-(2-chlorocarbonyl-2-cyano-vinyl)-indol-1-yl]-acetate (25 mg, 0.08 mmol) and DIEA (41 µl, 0.24 mmol) in dry dichloromethane (1 ml). The reaction mixture is stirred at rt overnight, then is washed with 1N aqueous HCl, water and saturated aqueous $NaHCO_3$ solution. The solvent of the organic phase is removed yielding crude subtitle compound: t_R (LC-2) 2.18 min (single peak); ESI-MS(+): *m/z* 374.45 $[M+H]^+$ (calcd 373.40 for $C_{22}H_{19}N_3O_3$).

Step B) A stirred solution of crude ethyl [3-(2-cyano-2-phenylcarbamoyl-vinyl)-indol-1-yl]-acetate (0.079 mmol) in THF (0.8 ml) is treated with 0.2N aqueous NaOH (0.4 ml, 0.08 mmol) at rt for 10 min. The yellow reaction mixture is diluted with water (2 ml) and washed twice with diethyl ether (2 ml). The aqueous phase is acidified to pH 1 by adding conc. HCl and extracted with dichloromethane. The solvent is evaporated and the residue is recrystallized from acetonitrile yielding pure title compound: t_R (LC-2) 1.91 min (single peak); ESI-MS(+): *m/z* 346.16 $[M+H]^+$ (calcd 345.35 for $C_{20}H_{15}N_3O_3$).

Alternatively to re-crystallization, final purification of the title compound is performed by column chromatography on silica gel (hexane/ EtOAc 3:1, containing 2% of AcOH), or by preparative reverersed-phase HPLC.

Alternatively, indolacetic acid derivative of the general Formula I is prepared as described below for Example 107, starting with the respective Precursor B and 2-cyano-acetamide reagent of Formula $NC\text{-}CH_2\text{-}CONR^5R^6$.

Example 107

[5-Bromo-3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-indol-1-yl]-acetic acid

Step c) Ethyl [5-bromo-3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-indol-1-yl]-acetate: A mixture of 2-cyano-*N*-phenyl-acetamide (122 mg, 0.14 mmol) and sodium ethylate (9.3 mg, 0.14 mmol) in dry ethanol (1 ml) is ultra-sonicated for 2 min and then added to a solution of 5-bromo-1-ethoxycarbonylmethyl-3-pyrrolidin-1-ylmethylene-3*H*-indolium bromide (50 mg, 0.14 mmol) in dry ethanol (1 ml). The reaction mixture is stirred at rt for 15 min, the precipitate is filtered off and washed twice with a small amount of ethanol. Pure subtitle compound is obtained as a brownish solid (24 mg) in 39% yield: t_R (LC-2) 2.51 min; ESI-MS(+): *m/z* 454.09 $[M+2]^+$ (calcd 452.30 for $C_{22}H_{18}BrN_3O_3$).

Step b) The title compound is obtained using conditions for the hydrolysis of the above ester analogous to Example 1: t_R (LC-2) 2.25 min; ESI-MS(+): *m/z* 424.08 $[M+H]^+$ (calcd 423.03 for $C_{20}H_{14}BrN_3O_3$).

Preparation of 2-cyano-acetamide reagent of Formula $NC\text{-}CH_2\text{-}CONR^5R^6$:

2-Cyano-*N*-phenyl-acetamide

Cyanoacetic acid (1.0 g, 11.7 mmol) is added to a stirred suspension of PCl_5 (2.4 g, 11.7 mmol) in dry dichloromethane (200 ml). The reaction mixture is heated to reflux and kept stirring for 30 min. After cooling to rt, aniline (1.07 ml, 11.7 mmol) is added dropwise and the reaction is stirred at reflux for additional 2 h, then cooled to 0°C and neutralized by addition of aqueous saturated Na_2CO_3 solution. The precipitate is filtered off, washed with water and dried under high vacuum to give title compound (1.54 g) as a white solid in 82% yield: t_R (LC-2) 1.50 min; ESI-MS(+): *m/z* 183.33 $[M+Na]^+$ (calcd 160.17 for $C_9H_8N_2O$).

Phenethyl-phenyl-amine ($HNR^{11}R^{12}$ for Example 84)

Sodium triacetoxyborohydride (5.46 g, 26 mmol) is added in small portions to a stirred solution of aniline (2.0 g, 21.5 mmol) and phenylacetaldehyde (2.83 g, 24 mmol) in dry DMF/ MeOH/ AcOH (87:10:3, 120 ml). After stirring at rt for 90 min, the volatiles are removed under reduced pressure. The residue is dissolved in dichloromethane (200 ml) and extracted twice with 1 N HCl. The combined aqueous layers are washed with EtOAc, then ammonium hydroxide solution is added to pH 9, and the mixture is extracted with dichloromethane. The solvent is evaporated, and the crude product is purified by silica gel chromatography (hexane/ EtOAc, 5:1) affording pure title compound as a yellow oil: t_R (LC-2) 2.16 min; ESI-MS (positive ion) *m/z* 198.22 $[M+H]^+$ (calcd 197.28 for $C_{14}H_{15}N$).

5,6,11,12-tetrahydro-dibenzo[b,f]azocine ($HNR^{11}R^{12}$ for Example 85)

To a suspension of 11,12-dihydro-5H-dibenzo[b,f]azocin-6-one (2.0 g, 8.96 mmol) in dry THF (20 ml) is added dropwise a solution of $LiAlH_4$ (1.0 N in THF, 8.96 ml) over a period of 10 min. After ceasing of gas evolution, the reaction mixture is kept stirring at reflux overnight, then quenched by the addition of water (0.48 ml). The precipitate is filtered off and the filtrate is extracted twice with EtOAc. The combined organic layers are dried over Na_2SO_4, the solvent is evaporated and the residue recrystallized from boiling hexane to give off white crystals of the title compound (1.35 g) in 72% yield: t_R (LC-2) 1.65 min; ESI-MS(+): *m/z* 210.70 $[M+H]^+$ (calcd 209.29 for $C_{15}H_{15}N$).

6,11-Dihydro-5H-dibenzo[b,e]azepine ($HNR^{11}R^{12}$ for Example 89)

i) 5,11-Dihydro-dibenzo[b,e]azepin-6-one:

A suspension of anhydrous aluminum chloride (319 mg, 2.39 mmol) in *o*-xylene is heated to 110°C. Then, a solution of 2-benzylphenylisocyanate (500 mg, 2.39 mmol) is added dropwise and the brown reaction mixture is kept stirring at 150°C during 1h. After cooling to rt, the solvent is evaporated, the residue is dissolved in dichloromethane/ methanol (19:1) and filtered through a small plug of silica gel. The solvent is evaporated and the crude product is recrystallized from acetonitrile to give pure subtitle compound

as a beige solid (170 mg) in 34% yield (Warawa et al., *J. Med. Chem.* **2001**, *44*, 372-389.): t_R (LC-2) 1.87 min; ESI-MS(+): *m/z* 210.13 $[M+H]^+$ (calcd 209.24 for $C_{14}H_{11}NO$).

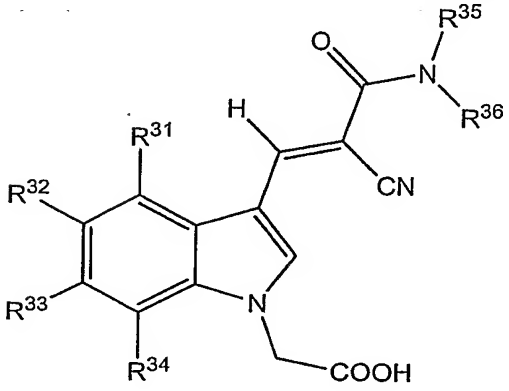
ii) To a stirred solution of 55,11-dihydro-dibenzo[b,e]azepin-6-one (170 mg, 0.81 mmol) in dry THF (20 ml) is added dropwise a solution of $LiAlH_4$ (1.0 N in THF, 0.81 mmol) over a period of 10 min. After ceasing of gas evolution the reaction mixture is kept stirring at reflux overnight, cooled to rt and poured onto water (100 ml). The mixture is extracted with diethyl ether, the combined organic layers are dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue is recrystallized from boiling hexane affording title compound as an off white solid (130 mg) in 82% yield: t_R (LC-2) 2.09 min; ESI-MS(+): *m/z* 197.33 $[M+2H]^+$ (calcd 195.26 for $C_{14}H_{13}N$).

Diphenethyl-amine ($HNR^{11}R^{12}$ for Example 90)

Sodiumtriacetoxyborohydride (8.87 g, 41.3 mmol) is added in small portions at 0°C to a stirred solution of phenethylamine (5.0 g, 41.3 mmol) and phenylacetaldehyde (4.96 g, 41.3 mmol) in methanol (50 ml). The reaction mixture is stirred at rt overnight, poured onto saturated aqueous KH_2PO_4 solution and extracted twice with EtOAc. The solvent is evaporated, the residue is taken up in 1N HCl and washed twice with dichloromethane. The aqueous layer is adjusted to pH 9 by the addition of ammonium hydroxide solution and extracted with dichloromethane. Drying the combined organic layers over Na_2SO_4 and evaporating the solvents give crude title compound as a pale yellow oil: t_R (LC-2) 1.40 min; ESI-MS(+): *m/z* 226.23 $[M+H]^+$ (calcd 225.33 for $C_{16}H_{19}N$).

Examples 2-112 of the following Tables 1, 2, 3 and 4 are prepared using a procedure analogous to that described for Example 1, or analogous to that described for Example 107, substituting the appropriate amine for aniline.

Table 1: Examples 1-106 with the general structure of



IV

Formula IV, wherein R^{31}= R^{32}= R^{33}= R^{34}= H.

Ex.	Name	R^{35}	R^{36}	Formula Mol weight	t_R [min] (Meth.)	MS Data *m/z* $[M+H]^+$
1	[3-((E)-2-Cyano-2-phenylcarbamoyl-vinyl)-indol-1-yl]-acetic acid	H	phenyl	C20H15N3O3 345.357	1.91 (LC-2)	346.16
2	[3-((E)-2-Cyano-2-m-tolylcarbamoyl-vinyl)-indol-1-yl]-acetic acid	H	3-methyl-phenyl	C21H17N3O3 359.384	2.22 (LC-1)	260.20
3	{3-[(E)-2-Cyano-2-(4-methoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	4-methoxy-phenyl	C21H17N3O4 375.383	2.10 (LC-1)	376.25
4	{3-[(E)-2-(3-Bromo-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	3-bromo-phenyl	C20H14N3O3Br 424.253	2.34 (LC-1)	426.00

5	{3-[(E)-2-Cyano-2-(cyclohexylmethyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	cyclohexyl-methyl	C21H23N3O3 365.432	2.08 (LC-2)	366.24
6	[3-((E)-2-Cyano-2-phenethylcarbamoyl-vinyl)-indol-1-yl]-acetic acid	H	phenethyl	C22H19N3O3 373.411	1.94 (LC-2)	374.20
7	[3-((E)-2-Cyano-2-isopropylcarbamoyl-vinyl)-indol-1-yl]-acetic acid	H	isopropyl	C17H17N3O3 311.34	1.73 (LC-2)	312.23
8	[3-((E)-2-Cyano-2-propylcarbamoyl-vinyl)-indol-1-yl]-acetic acid	H	propyl	C17H17N3O3 311.34	1.73 (LC-2)	312.23
9	[3-((E)-2-Cyano-2-cyclohexylcarbamoyl-vinyl)-indol-1-yl]-acetic acid	H	cyclohexyl	C20H21N3O3 351.405	1.96 (LC-2)	352.26
10	{3-[(E)-2-Cyano-2-(3-methyl-butylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	3-methyl-butyl	C19H21N3O3 339.394	1.96 (LC-2)	340.20
11	[3-((E)-2-Benzylcarbamoyl-2-cyano-vinyl)-indol-1-yl]-acetic acid	H	benzyl	C21H17N3O3 359.384	1.91 (LC-2)	360.21

12	{3-[(E)-2-(Benzyl-phenyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	phenyl	benzyl	C27H21N3O3 435.482	2.34 (LC-1)	436.26
13	{3-[(E)-2-Cyano-2-(4-cyano-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	4-cyano-phenyl	C21H14N4O3 370.367	2.15 (LC-1)	371.09
14	[3-((E)-2-Cyano-2-o-tolylcarbamoyl-vinyl)-indol-1-yl]-acetic acid	H	o-tolyl	C21H17N3O3 359.384	2.14 (LC-1)	360.26
15	{3-[(E)-2-Cyano-2-(4-ethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	4-ethyl-phenyl	C22H19N3O3 373.411	2.33 (LC-1)	374.21
16	{3-[(E)-2-Cyano-2-(4-fluoro-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	4-fluoro-phenyl	C20H14N3O3F 363.347	2.16 (LC-1)	364.21
17	{3-[(E)-2-Cyano-2-(4-phenoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	4-phenoxy-phenyl	C26H19N3O4 437.454	2.42 (LC-1)	438.30
18	{3-[(E)-2-Cyano-2-(naphthalen-2-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	naphthalen-2-yl	C24H17N3O3 395.417	2.33 (LC-1)	396.32

19	{3-[(E)-2-Cyano-2-(2-isopropyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	2-isopropyl-phenyl	C23H21N3O3 387.438	2.27 (LC-1)	388.23
20	[3-((E)-2-Cyano-2-p-tolylcarbamoyl-vinyl)-indol-1-yl]-acetic acid	H	p-tolyl	C21H17N3O3 359.384	2.23 (LC-1)	360.26
21	{3-[(E)-2-Cyano-2-(4-isopropyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	4-isopropyl-phenyl	C23H21N3O3 387.438	2.40 (LC-1)	388.29
22	{3-[(E)-2-Cyano-2-(3-methoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	3-methoxy-phenyl	C21H17N3O4 375.383	2.16 (LC-1)	376.12
23	{3-[(E)-2-Cyano-2-(3-fluoro-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	3-fluoro-phenyl	C20H14N3O3F 363.347	2.21 (LC-1)	364.15
24	{3-[(E)-2-Cyano-2-(9H-fluoren-2-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	9H-fluoren-2-yl	C27H19N3O3 433.466	2.47 (LC-1)	434.22
25	{3-[(E)-2-Cyano-2-(4-propyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	4-propyl-phenyl	C23H21N3O3 387.438	2.43 (LC-1)	388.16

26	{3-[(E)-2-(Biphenyl-4-ylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	biphenyl-4-yl	C26H19N3O3 421.455	2.44 (LC-1)	422.24
27	{3-[(E)-2-Cyano-2-(3,2'-dimethyl-biphenyl-4-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	3,2'-dimethyl-biphenyl-4-yl	C28H23N3O3 449.509	2.53 (LC-1)	450.15
28	{3-[(E)-2-(4-tert-Butyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	4-tert-butyl-phenyl	C24H23N3O3 401.465	2.46 (LC-1)	402.24
29	{3-[(E)-2-(2-Benzyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	2-benzyl-phenyl	C27H21N3O3 435.482	2.35 (LC-1)	436.13
30	{3-[(E)-2-(4-Butyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	4-butyl-phenyl	C24H23N3O3 401.465	2.52 (LC-1)	402.37
31	{3-[(E)-2-(2-Acetyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	2-acetyl-phenyl	C22H17N3O4 387.394	2.24 (LC-1)	388.16
32	{3-[(E)-2-Cyano-2-(indan-5-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	indan-5-yl	C23H19N3O3 385.422	2.36 (LC-1)	386.19

33	{3-[(E)-2-(4-sec-Butyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	4-sec-butyl-phenyl	C24H23N3O3 401.465	2.51 (LC-1)	402.24
34	{3-[(E)-2-Cyano-2-(4-ethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	4-ethoxy-phenyl	C22H19N3O4 389.41	2.20 (LC-1)	390.20
35	{3-[(E)-2-Cyano-2-(3-ethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	3-ethoxy-phenyl	C22H19N3O4 389.41	2.25 (LC-1)	390.14
36	{3-[(E)-2-Cyano-2-(2-propyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	2-propyl-phenyl	C23H21N3O3 387.438	2.33 (LC-1)	388.23
37	{3-[(E)-2-Cyano-2-(3-phenoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	3-phenoxy-phenyl	C26H19N3O4 437.454	2.44 (LC-1)	438.18
38	{3-[(E)-2-Cyano-2-(3-ethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	3-ethyl-phenyl	C22H19N3O3 373.411	2.33 (LC-1)	374.21
39	{3-[(E)-2-Cyano-2-(2-ethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	2-ethoxy-phenyl	C22H19N3O4 389.41	2.39 (LC-1)	390.20

40	{3-[(E)-2-(3-Benzyloxy-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	3-benzyloxy-phenyl	C27H21N3O4 451.481	2.42 (LC-1)	452.19
41	{3-[(E)-2-(4-Bromo-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	4-bromo-phenyl	C20H14N3O3Br 424.253	2.33 (LC-1)	424.09
42	{3-[(E)-2-Cyano-2-(4-iodo-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	4-iodo-phenyl	C20H14N3O3I 471.249	2.37 (LC-1)	472.00
43	{3-[(E)-2-Cyano-2-(3-iodo-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	3-iodo-phenyl	C20H14N3O3I 471.249	2.37 (LC-1)	472.00
44	(3-{(E)-2-Cyano-2-[(4-fluoro-phenyl)-methyl-carbamoyl]-vinyl}-indol-1-yl)-acetic acid	methyl	4-fluoro-phenyl	C21H16N3O3F 377.374	2.08 (LC-1)	378.22
45	(3-{(E)-2-Cyano-2-[(4-methoxy-phenyl)-methyl-carbamoyl]-vinyl}-indol-1-yl)-acetic acid	methyl	4-methoxy-phenyl	C22H19N3O4 389.41	2.06 (LC-1)	390.20
46	{3-[(E)-2-Cyano-2-(methyl-phenyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid	methyl	phenyl	C21H17N3O3 359.384	2.05 (LC-1)	360.20

47	{3-[(E)-2-Cyano-3-(3,4-dihydro-2H-quinolin-1-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid	3,4-dihydro-2H-quinolin-1-yl		C23H19N3O3 385.422	2.16 (LC-1)	386.25
48	{3-[(E)-2-Cyano-2-(methyl-p-tolyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid	methyl	p-tolyl	C22H19N3O3 373.411	2.14 (LC-1)	374.21
49	(3-{(E)-2-Cyano-2-[2-(2,4-dichloro-phenoxy)-phenylcarbamoyl]-vinyl}-indol-1-yl)-acetic acid	H	2,4-dichloro-phenoxy)-phenyl	C26H17N3O4Cl2 506.344	2.25 (LC-1)	374.15
50	{3-[(E)-2-Cyano-2-(2,5-dimethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	2,5-dimethyl-phenyl	C22H19N3O3 373.411	2.25 (LC-1)	374.15
51	{3-[(E)-2-Cyano-2-(9-ethyl-9H-carbazol-3-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	9-ethyl-9H-carbazol-3-yl	C28H22N4O3 462.508	2.48 (LC-1)	463.21
52	{3-[(E)-2-(3,5-Bis-trifluoromethyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	3,5-bis-trifluoromethyl-phenyl	C22H13N3O3F6 481.351	2.56 (LC-1)	482.07
53	{3-[(E)-2-Cyano-2-(5-methoxy-2-methyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	5-methoxy-2-methyl-phenyl	C22H19N3O4 389.41	2.16 (LC-1)	390.14

54	{3-[(E)-2-(3-Benzoyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	3-benzoyl-phenyl	C27H19N3O4 449.465	2.33 (LC-1)	450.09
55	{3-[(E)-2-(4-Benzyloxy-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	4-benzyloxy-phenyl	C27H21N3O4 451.481	2.40 (LC-1)	452.19
56	{3-[(E)-2-Cyano-2-(3-nitro-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	3-nitro-phenyl	C20H14N4O5 390.354	2.20 (LC-1)	391.09
57	{3-[(E)-2-Cyano-2-(9-oxo-9H-fluoren-2-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	9-oxo-9H-fluoren-2-yl	C27H17N3O4 447.449	2.36 (LC-1)	448.05
58	{3-[(E)-2-Cyano-2-(4-methoxy-biphenyl-3-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	4-methoxy-biphenyl-3-yl	C27H21N3O4 451.481	2.56 (LC-1)	452.12
59	{3-[(E)-2-Cyano-2-(2-methoxy-dibenzofuran-3-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	2-methoxy-dibenzofuran-3-yl	C27H19N3O5 465.464	2.63 (LC-1)	466.14
60	{3-[(E)-2-Cyano-2-(9-oxo-9H-fluoren-4-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	9-oxo-9H-fluoren-4-yl	C27H17N3O4 447.449	2.22 (LC-1)	448.11

61	{3-[(E)-2-Cyano-2-(9-oxo-9H-fluoren-1-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	9-oxo-9H-fluoren-1-yl	C27H17N3O4 447.449	2.22 (LC-1)	448.11
62	{3-[(E)-2-(2-Benzoyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	2-benzoyl-phenyl	C27H19N3O4 449.465	2.43 (LC-1)	450.15
63	{3-[(E)-2-(3-Chloro-4-methoxy-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	3-chloro-4-methoxy-phenyl	C21H16N3O4Cl 409.828	2.21 (LC-1)	410.08
64	{3-[(E)-2-(5-Chloro-2-methoxy-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	5-chloro-2-methoxy-phenyl	C21H16N3O4Cl 409.828	2.45 (LC-1)	410.08
65	3-[(E)-3-(1-Carboxymethyl-1H-indol-3-yl)-2-cyano-acryloylamino]-4-methyl-benzoic acid methyl ester	H	2-methyl-5-methoxycarbonyl-phenyl	C23H19N3O5 417.42	2.15 (LC-1)	418.10
66	{3-[(E)-2-(4-Chloro-2-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	4-chloro-2-methyl-phenyl	C21H16N3O3Cl 393.829	2.31 (LC-1)	394.09
67	2-[(E)-3-(1-Carboxymethyl-1H-indol-3-yl)-2-cyano-acryloylamino]-benzoic acid methyl ester	H	2-methoxy-carbonyl-phenyl	C22H17N3O5 403.393	2.35 (LC-1)	426.13 $[M+Na]^+$

68	{3-[(E)-2-Cyano-2-(4-trifluoromethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	4-trifluoro-methoxy-phenyl	C21H14N3O4F3 429.353	2.37 (LC-1)	430.08
69	{3-[(E)-2-Cyano-2-(3,5-dimethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	3,5-dimethyl-phenyl	C22H19N3O3 373.411	2.33 (LC-1)	374.15
70	{3-[(E)-2-(3-Bromo-4-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	3-bromo-4-methyl-phenyl	C21H16N3O3Br 438.28	2.41 (LC-1)	438.04
71	{3-[(E)-2-(4-Bromo-3-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	4-bromo-3-methyl-phenyl	C21H16N3O3Br 438.28	2.42 (LC-1)	440.02
72	4-[(E)-3-(1-Carboxymethyl-1H-indol-3-yl)-2-cyano-acryloylamino]-benzoic acid ethyl ester	H	4-ethoxycarbonyl-phenyl	C23H19N3O5 417.42	2.27 (LC-1)	418.10
73	3-[(E)-3-(1-Carboxymethyl-1H-indol-3-yl)-2-cyano-acryloylamino]-benzoic acid methyl ester	H	3-methoxycarbonyl-phenyl	C22H17N3O5 403.393	2.15 (LC-1)	404.09
74	{3-[(E)-2-Cyano-2-(4-trifluoromethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	4-trifluoromethyl-phenyl	C21H14N3O3F3 413.354	2.36 (LC-1)	414.09

75	{3-[(E)-2-Cyano-2-(3,5-dimethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	3,5-dimethoxy-phenyl	C22H19N3O5 405.409	2.18 (LC-1)	406.13
76	{3-[(E)-2-(4-Bromo-3-chloro-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	4-bromo-3-chloro-phenyl	C20H13N3O3BrCl 458.698	2.45 (LC-1)	459.96
77	{3-[(E)-2-(4-Bromo-2-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	4-bromo-2-methyl-phenyl	C21H16N3O3Br 438.28	2.35 (LC-1)	440.02
78	{3-[(E)-2-(4-Acetyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	4-acetyl-phenyl	C22H17N3O4 387.394	2.06 (LC-1)	388.16
79	{3-[(E)-2-(2-Bromo-4-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	2-bromo-4-methyl-phenyl	C21H16N3O3Br 438.28	2.41 (LC-1)	440.02
80	{3-[(E)-2-(Benzo[1,3]dioxol-5-ylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	H	benzo[1,3]dioxol-5-yl	C21H15N3O5 389.366	2.10 (LC-1)	390.07
81	{3-[(E)-2-Cyano-2-(2,3-dihydro-benzo[1,4]dioxin-6-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	2,3-dihydro-benzo[1,4]dioxin-6-yl	C22H17N3O5 403.393	2.08 (LC-1)	404.09

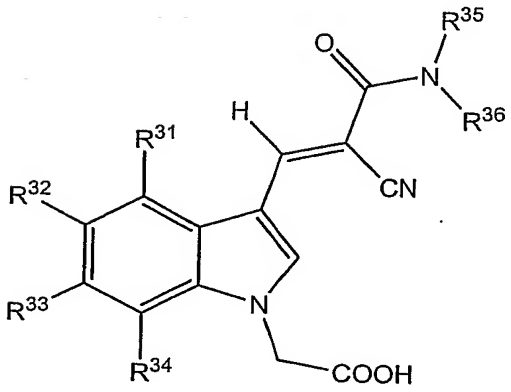
82	{3-[(E)-2-Cyano-2-(2-methoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	2-methoxy-phenyl	C21H17N3O4 375.383	2.28 (LC-1)	376.31
83	{3-[(E)-2-Cyano-2-(2-phenoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid	H	2-phenoxy-phenyl	C26H19N3O4 437.454	2.48 (LC-1)	438.24
84	Sodium {3-[(E)-2-cyano-2-(phenethyl-phenyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid	phenyl	phenethyl	C28H22N3O3Na 471.491	2.37 (LC-1)	450.15
85	Sodium {3-[(E)-2-cyano-3-(11,12-dihydro-6H-dibenzo[b,f]azocin-5-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid	11,12-dihydro-6H-dibenzo[b,f]azocin-5-yl		C29H22N3O3Na 483.502	2.33 (LC-1)	462.19
86	Sodium [3-((E)-2-cyano-2-diphenylcarbamoyl-vinyl)-indol-1-yl]-acetic acid	phenyl	phenyl	C26H18N3O3Na 443.437	2.20 (LC-1)	422.12
87	Sodium [3-((E)-2-cyano-3-dibenzo[b,f]azepin-5-yl-3-oxo-propenyl)-indol-1-yl]-acetate	dibenzo[b,f]azepin-5-yl		C28H18N3O3Na 467.459	2.26 (LC-1)	446.14
88	Sodium (3-{(E)-2-[(4-chloro-phenyl)-methyl-carbamoyl]-2-cyano-vinyl}-indol-1-yl)-acetic acid	methyl	4-chloro-phenyl	C21H15N3O3ClNa 415.811	2.14 (LC-1)	416.06

89	{3-[(E)-2-Cyano-3-(6,11-dihydro-dibenzo[b,e]azepin-5-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid	6,11-dihydro-dibenzo[b,e]azepin-5-yl		C28H21N3O3 447.493	2.31 (LC-1)	448.24
90	[3-((E)-2-Cyano-2-diphenethylcarbamoyl-vinyl)-indol-1-yl]-acetic acid	phenethyl	phenethyl	C30H27N3O3 477.562	2.40 (LC-1)	478.31
91	{3-[(E)-2-Cyano-3-(10,11-dihydro-dibenzo[b,f]azepin-5-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid	10,11-dihydro-dibenzo[b,f]azepin-5-yl		C28H21N3O3 447.493	2.27 (LC-1)	448.30
92	(3-{(E)-2-Cyano-2-[methyl-((R)-1-phenyl-ethyl)-carbamoyl]-vinyl}-indol-1-yl)-acetic acid	methyl	(R)-1-phenyl-ethyl	C23H21N3O3 387.438	2.23 (LC-1)	388.23
93	{3-[(E)-2-(Benzyl-methyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	methyl	benzyl	C22H19N3O3 373.411	2.13 (LC-1)	374.21
94	(3-{(E)-2-[(4-Acetyl-phenyl)-methyl-carbamoyl]-2-cyano-vinyl}-indol-1-yl)-acetic acid	methyl	4-acetyl-phenyl	C23H19N3O4 401.421	2.00 (LC-1)	402.18
95	(3-{(E)-2-[(4-Acetyl-phenyl)-furan-2-ylmethyl-carbamoyl]-2-cyano-vinyl}-indol-1-yl)-acetic acid	furan-2-ylmethyl	4-acetyl-phenyl	C27H21N3O5 467.48	2.15 (LC-1)	468.07

96	{3-[(E)-2-(Benzyl-carboxymethyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	benzyl	carboxy-methyl	C23H19N3O5 417.42	2.01 (LC-1)	416.19 $[M-H]^-$
97	3-{Benzyl-[(E)-3-(1-carboxymethyl-1H-indol-3-yl)-2-cyano-acryloyl]-amino}-propionic acid	benzyl	carboxyethyl	C24H21N3O5 431.447	1.97 (LC-1)	432.18
98	{3-[(E)-2-Cyano-3-(2,3-dihydro-indol-1-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid	2,3-dihydro-indol-1-yl		C22H17N3O3 371.395	2.2 (LC-1)	372.19
99	{3-[(E)-2-(Carboxymethyl-phenyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	phenyl	carboxy-methyl	C22H17N3O5 403.393	1.86 (LC-1)	402.11 $[M-H]^-$
100	(3-{(E)-2-Cyano-2-[(2-cyano-ethyl)-phenyl-carbamoyl]-vinyl}-indol-1-yl)-acetic acid	phenyl	2-cyano-ethyl	C23H18N4O3 398.421	2.01 (LC-1)	399.18
101	(3-{(E)-2-[(3-Chloro-phenyl)-methyl-carbamoyl]-2-cyano-vinyl}-indol-1-yl)-acetic acid	methyl	3-chloro-phenyl	C21H16N3O3Cl 393.829	2.14 (LC-1)	394.15
102	{3-[(E)-2-(Allyl-phenyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	phenyl	allyl	C23H19N3O3 385.422	2.18 (LC-1)	386.19

103	{3-[(E)-2-Cyano-2-(cyclohexyl-phenyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid	phenyl	cyclohexyl	C26H25N3O3 427.503	2.43 (LC-1)	428.23
104	{3-[(E)-2-Cyano-2-(methyl-o-tolyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid	methyl	o-tolyl	C22H19N3O3 373.411	2.09 (LC-1)	374.21
105	{3-[(E)-2-Cyano-2-(ethyl-phenyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid	phenyl	ethyl	C22H19N3O3 373.411	2.13 (LC-1)	374.21
106	{3-[(E)-2-(Butyl-phenyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid	phenyl	butyl	C24H23N3O3 401.465	2.34 (LC-1)	402.24

Table 2: Examples 107-109 with the general structure of



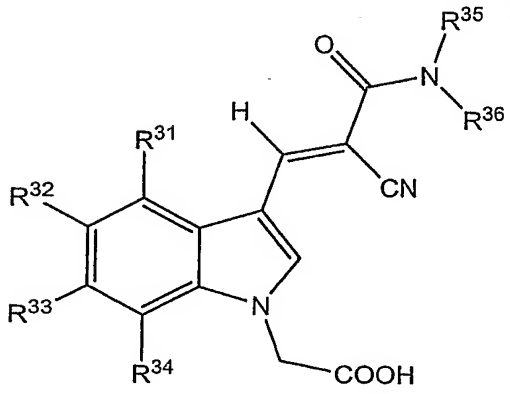
IV

Formula IV, wherein $R^{31}= R^{33}= R^{34}= H$.

Ex.	Name	R^{32}	R^{35}	R^{36}	Formula Mol weight	t_R [min] (Method)	MS Data *m/z* $[M+H]^+$
107	[5-Bromo-3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-indol-1-yl]-acetic acid	bromo	H	phenyl	C20H14N3O3Br 424.253	2.25 (LC-2)	448.04 $[M+Na]^+$
108	[3-((E)-2-Cyano-2-phenylcarbamoyl-vinyl)-5-fluoro-indol-1-yl]-acetic acid	fluoro	H	phenyl	C20H14N3O3F 363.347	2.13 (LC-2)	364.21
109	[3-((E)-2-Cyano-2-phenylcarbamoyl-vinyl)-5-methyl-indol-1-yl]-acetic acid	methyl	H	phenyl	C21H17N3O3 359.384	2.18 (LC-2)	360.20

5

Table 3: Examples 110-111 with the general structure of

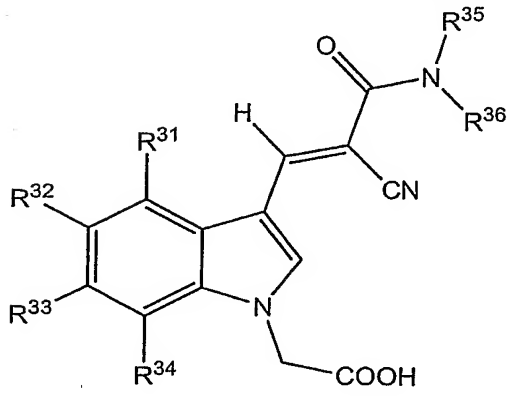


IV

Formula IV, wherein R^{31}= R^{32}= R^{34}= H.

Ex.	Name	R^{33}	R^{35}	R^{36}	Formula Mol weight	t_R [min] (Method)	MS Data *m/z* $[M+H]^+$
110	[3-((E)-2-Cyano-2-phenylcarbamoyl-vinyl)-6-fluoro-indol-1-yl]-acetic acid	fluoro	H	phenyl	C20H14N3O3F 363.347	2.14 (LC-2)	364.14
111	[3-((E)-2-Cyano-2-phenylcarbamoyl-vinyl)-6-nitro-indol-1-yl]-acetic acid	nitro	H	phenyl	C20H14N4O5 390.354	2.12 (LC-2)	391.22

Table 4: Example 112 with the general structure of



IV

Formula IV, wherein $R^{32}= R^{32}= R^{33}=$ H.

Ex.	Compound	R^{34}	R^{35}	R^{36}	Formula Mol weight	t_R [min] (Method)	MS Data *m/z* $[M+H]^+$
112	[3-((E)-2-Cyano-2-phenylcarbamoyl-vinyl)-7-methyl-indol-1-yl]-acetic acid	methyl	H	phenyl	C21H17N3O3 359.384	2.16 (LC-2)	360.20

Biological assays:

Example B-1

Preparation of CRTH2 membranes and radioligand binding assay:

Preparation of the membranes and radioligand binding assays are performed according to known procedures, e.g. Sawyer N. et al. (*Br. J. Pharmacol.*, 2002, 137, 1163-1172). A clonal HEK 293 cell line, expressing high level of recombinant hCRTH2 receptor, is selected for the preparation of membranes. Cells are detached from culture plates in 5 ml buffer A per plate (5 mM Tris, 1 mM $MgCl_2x6\ H_2O$, 0.1 mM PMSF, 0.1 mM phenanthroline) using a police rubber and transferred into centrifugation tubes and frozen at –80°C. After thawing, the cells are centrifuged at 500 g for 5 min and then resuspended in buffer A. Cells are then fragmented by homogenization with a Polytron homogenizer for 30 s. The membrane fragments are centrifuged at 3000 g for 40 min and resuspended in membranes in buffer B (50 mM Tris, 25 mM $MgCl_2$, 250 mM saccharose, pH 7.4) and aliquots are stored frozen.

Binding assay is performed in a total volume of 250 µl. In each well, 75 µl buffer C (50 mM Tris, 100 mM NaCl, 1 mM EDTA, 0.1% BSA (protease free), 0.01 % NaN_3, pH 7.4) was mixed with 50 µl $\{^3H\}$-PGD_2 (at 2.5 nM (220.000 dpm per well) from Amersham, TRK734), 100 µl CRTH2 membranes to give 80 µg per well and 25 µl of test compound in buffer C containing 1% DMSO. For unspecific binding, PGD2 is added to the reaction mixture at 1 µM final concentration. This binding assay mix is incubated at rt for 90 min and then filtered through a GF/C filter plate. The filter is washed three times with ice cold binding buffer. Then, 40 µl per well Microscint-40 (Packard) are added and the bound radioactivity is quantified by means of Topcount (Packard).

Example B-2

Intracellular calcium mobilization assay (FLIPR):

Cells (HEK-293), stably expressing the $hCRTH_2$ receptor under the control of the cytomegalovirus promotor from a single insertion of the expression vector pcDNA5 (Invitrogen), are grown to confluency in DMEM (low glucose, Gibco) medium

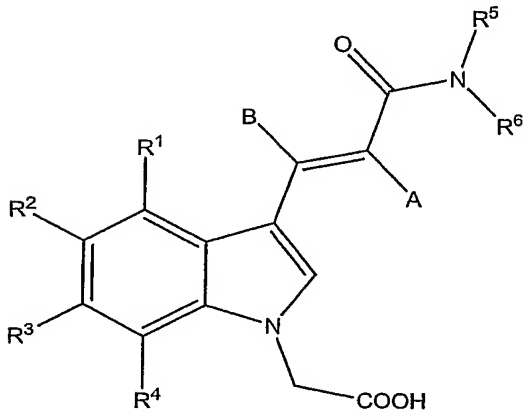
supplemented with 10% fetal calf serum (both Bioconcept, Switzerland) under standard mammalian cell culture conditions (37°C in a humidified atmosphere of 5% CO_2). Cells are detached from culture dishes using a dissociation buffer (0.02% EDTA in PBS, Gibco) for 1 min, and collected by centrifugation at 200g at rt for 5 min in assay buffer (equal parts of Hank's BSS (HBSS, Bioconcept) and DMEM (low glucose, without phenol red, Gibco)). After incubation for 45 min (37°C and 5% CO_2) in the presence of 1 μM Fluo-4 and 0.04% Pluronic F-127 (both Molecular Probes), 20mM HEPES (Gibco) in assay buffer, the cells are washed with and resuspended in assay buffer, then seeded onto 384-well FLIPR assay plates (Greiner) at 50,000 cells in 66μl per well), and sedimented by centrifugation.

Stock solutions of test compounds are made up at a concentration of 10 mM in DMSO, and serially diluted in assay buffer to concentrations required for inhibition dose response curves. Prostaglandin D_2 (Biomol, Plymouth Meeting, PA) is used as an agonist.

A FLIPR384 instrument (Molecular Devices) is operated according to the manufacturer's standard instructions, adding 4 µl of test compound dissolved at 10mM in DMSO and diluted prior to the experiment in assay buffer to obtain the desired final concentration. 10μl of 80 nM prostaglandin D_2 (Biomol, Plymouth Meeting, PA) in assay buffer, supplemented with 0.8% bovine serum albumin (fatty acid content <0.02%, Sigma), is then added to obtain a final concentration of 10nM and 0.1%, respectively. Changes in fluorescence are monitored before and after the addition of test compounds at λ_{ex}=488 nm and λ_{em}=540 nm. Emission peak values above base level after prostaglandin D_2 addition are exported after base line subtraction. Values are normalized to high-level control (no test compound added) after subtraction of base line value (no prostaglandin D_2 added). The program XLlfit 3.0 (IDBS) is used to fit the data to a single site dose response curve of the equation (A+((B-A)/(1+((C/x)^D)))) and to calculate the IC_{50} values.

Claims:

1. Pharmaceutical compositions containing at least one compound of the indol-1-yl-acetic acids of the general Formula I



I

wherein

A represents hydrogen; lower alkyl; halogen or cyano;

B represents hydrogen; lower alkyl or halogen;

R^1, R^2, R^3 and R^4 independently represent hydrogen; lower alkyl; halogen; nitro; cyano or formyl;

R^5 and R^6 independently represent hydrogen; lower alkyl; lower alkenyl; aryl; lower alkoxy-aryl; lower alkoxycarbonyl-aryl; lower alkylcarbonyl-aryl; aryl-lower alkoxy-aryl; aryl-lower alkyl; aryl-lower alkyl-aryl; arylcarbonyl-aryl; aryloxy-aryl; whereby the aryl group is unsubstituted or mono- or di-substituted with lower alkyl, lower alkoxy, halogen, cyano, lower alkoxycarbonyl, lower alkylcarbonyl, phenyl, benzyl, benzoyl, benzyloxy, benzyloxycarbonyl, trifluormethyl or trifluormethoxy; cyclolalkyl or heteroaryl;

R^5 and R^6, together with the nitrogen atom to which they are attached, form a heterocyclic ring system;

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, meso forms, geometric isomers,
prodrugs of compounds in which a prodrug forming group is present, as well as solvates and morphological forms, pharmaceutically acceptable salts thereof and usual inert carrier materials or adjuvants.

2. Pharmaceutical compositions according to claim 1 containing at least one compound of the indol-1-yl-acetic acids of the general Formula I for the prevention and treatment of diseases which are to be cured with CRTH2 receptor antagonists comprising the prevention and treatment of chronic and acute allergic immune disorders.

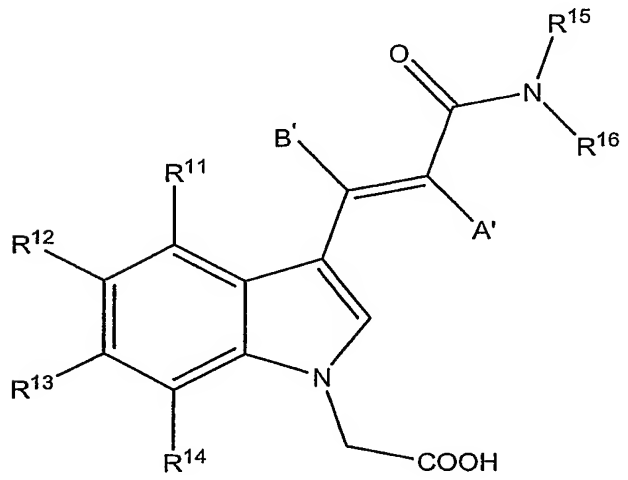
3. Pharmaceutical compositions according to claim 1 containing at least one compound of the indol-1-yl-acetic acids of the general Formula I for the prevention and treatment of chronic and acute allergic immune disorders comprising allergic asthma, rhinitis, chronic obstructive pulmonary disease (COPD), dermatitis, inflammatory bowel disease, rheumatoid arthritis, allergic nephritis, conjunctivitis, atopic dermatitis, bronchial asthma, food allergy, systemic mast cell disorders, anaphylactic shock, urticaria, eczema, itching, inflammation, ischemia-reperfusion injury, cerebrovascular disorders, pleuritis, ulcerative colitis, eosinophil-related diseases comprising Churg-Strauss syndrome and sinusitis, basophil-related diseases, comprising basophilic leukemia and basophilic leukocytosis in humans and other mammals.

4. Use of a pharmaceutical composition according to claim 1 containing at least one compound of the indol-1-yl-acetic acids of the general Formula I for the prevention and treatment of diseases which are to be cured with CRTH2 receptor antagonists comprising the prevention and treatment of chronic and acute allergic immune disorders.

5. Use of a pharmaceutical composition according to claim 1 containing at least one compound of the indol-1-yl-acetic acids of the general Formula I for the prevention and treatment chronic and acute allergic immune disorders comprising allergic asthma,

rhinitis, chronic obstructive pulmonary disease (COPD), dermatitis, inflammatory bowel disease, rheumatoid arthritis, allergic nephritis, conjunctivitis, atopic dermatitis, bronchial asthma, food allergy, systemic mast cell disorders, anaphylactic shock, urticaria, eczema, itching, inflammation, ischemia-reperfusion injury, cerebrovascular disorders, pleuritis, ulcerative colitis, eosinophil-related diseases comprising Churg-Strauss syndrome and sinusitis, basophil-related diseases, comprising basophilic leukemia and basophilic leukocytosis in humans and other mammals.

6. Novel compounds of the general Formula II



II

wherein

A' represents hydrogen; lower alkyl; halogen or cyano;

B' represents hydrogen; lower alkyl or halogen;

R^{11}, R^{12}, R^{13} and R^{14} independently represent hydrogen; lower alkyl; halogen; nitro; cyano or formyl;

R^{15} and R^{16} independently represent hydrogen; lower alkyl; lower alkenyl; aryl; lower alkoxy-aryl; lower alkoxycarbonyl-aryl; lower alkylcarbonyl-aryl; aryl-lower alkoxy-aryl; aryl-lower alkyl; aryl-lower alkyl-aryl; arylcarbonyl-aryl; aryloxy-aryl; whereby the aryl group is unsubstituted or mono- or di-substituted with lower alkyl, lower alkoxy,

halogen, cyano, lower alkoxycarbonyl, lower alkylcarbonyl, phenyl, benzyl, benzoyl, benzyloxy, benzyloxycarbonyl, trifluormethyl or trifluormethoxy; cyclolalkyl or heteroaryl;

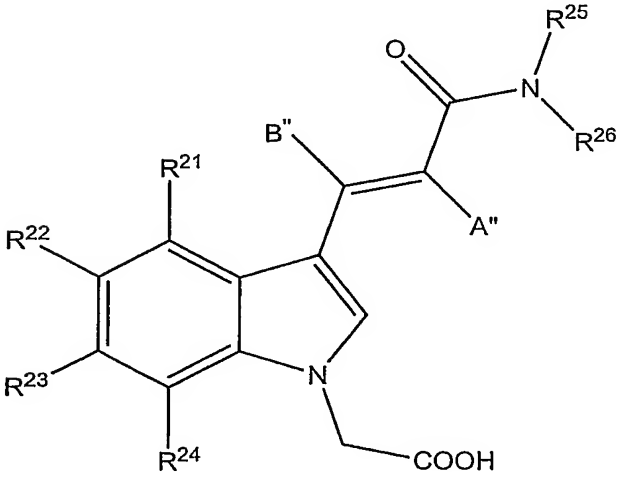
R^{15} and R^{16}, together with the nitrogen atom to which they are attached, form a heterocyclic ring system;

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, meso forms, geometric isomers,

prodrugs of compounds in which a prodrug forming group is present, as well as solvates and morphological forms and pharmaceutically acceptable salts thereof ;

with the proviso that the substituents R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} all at the same time do not represent hydrogen or in addition and in case either one of the substituents R^{15} or R^{16} represents hydrogen and the other aryl then the aryl group is not an unsubstituted indol-3-yl-ethyl, benzyl, or phenyl group, and also not a C1-C3 alkyl, C1-C2 alkoxy or halogen mono-substituted phenyl group, or R15 and R16 together with the nitrogen atom to which they are attached do not form a. phenyl substituted piperazine ring.

7. Novel compounds of the general Formula III,



III

wherein

A'' represents hydrogen; methyl; trifluoromethyl; chloro; or cyano;

B'' represents hydrogen; methyl; trifluoromethyl; or chloro;

R^{21}, R^{22}, R^{23} and R^{24} represent independently hydrogen; lower alkyl; halo-lower alkyl; lower alkoxy; halogen; nitro; cyano or formyl;

R^{25} and R^{26} represent independently hydrogen, lower alkenyl, alkoxy-aryl, alkoxycarbonyl-aryl, lower alkyl, alkylcarbonyl-aryl, arylalkoxy-aryl, arylalkyl, arylalkyl-aryl, aryl, arylcarbonyl-aryl, aryloxy-aryl, cyclolalkyl, heteroaryl;

R^{25} and R^{26}, together with the nitrogen atom to which they are attached, form a heterocyclic ring system with 3 to 15 ring atoms;

R^{25} represents hydrogen; lower alkyl; or arylalkyl; and

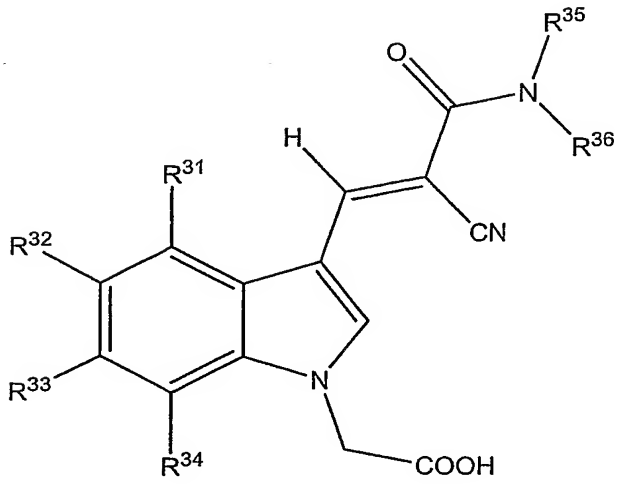
R^{26} represents lower alkyl; alkoxy-aryl; alkoxycarbonyl-aryl; alkylcarbonyl-aryl; arylalkoxy-aryl; arylalkyl; arylalkyl-aryl; arylcarbonyl-aryl; aryloxy-aryl; cyclylalkyl.

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, meso forms, geometric isomers,

prodrugs of compounds in which a prodrug forming group is present, as well as solvates and morphological forms and pharmaceutically acceptable salts thereof ;

with the proviso that the substituents R^{21}, R^{22}, R^{23}, R^{24}, R^{25} and R^{26} all at the same time do not represent hydrogen or in addition and in case either one of the substituents R^{25} or R^{26} represents hydrogen and the other aryl then the aryl group is not an unsubstituted indol-3-yl-ethyl, benzyl, or phenyl group, and also not a C1-C3 alkyl, C1-C2 alkoxy or halogen mono-substituted phenyl group, or R^{25} and R^{26} together with the nitrogen atom to which they are attached do not form a. phenyl substituted piperazine ring.

8. Novel compounds of Formula IV



IV

wherein

R^{31}, R^{32}, R^{33} and R^{34} represent independently methyl; trifluoromethyl; methoxy; fluoro, chloro;

R^{35} and R^{36}, together with the nitrogen atom to which they are attached, form a acridine, azepine, azocine, carbazole, indole, phenanthiridine or quinoline ring; or

R^{35} represents hydrogen,

R^{36} represents 2-ethoxy-phenyl; 2-methoxycarbonyl-phenyl, 2-methyl-5-methoxycarbonyl-phenyl, 3-methoxycarbonyl-phenyl, 4-ethoxycarbonyl-phenyl; 3-methyl-butyl, propyl; 2-acetyl-phenyl, 4-acetyl-phenyl; 3-benzyloxy-phenyl, 4-benzyloxy-phenyl; benzyl, phenethyl; 2-benzyl-phenyl; 2-benzoyl-phenyl, 3-benzoyl-phenyl; 2,3-dihydro-benzo[1,4]dioxin-6-yl, 2,5-dimethyl-phenyl, 2-bromo-4-methyl-phenyl, 2-isopropyl-phenyl, 2-methoxy-dibenzofuran-3-yl, 2-methoxy-phenyl, 2-propyl-phenyl, 3,2'-dimethyl-biphenyl-4-yl, 3,5-bis-trifluoromethyl-phenyl, 3,5-dimethoxy-phenyl, 3,5-dimethyl-phenyl, 3-bromo-4-methyl-phenyl, 3-bromophenyl, 3-chloro-4-methoxy-phenyl, 3-ethyl-phenyl, 3-fluoro-phenyl, 3-iodo-phenyl, 3-methoxy-phenyl, 3-nitro-phenyl, 4-bromo-2-methyl-phenyl, 4-bromo-3-chloro-phenyl, 4-bromo-3-methyl-phenyl, 4-butyl-phenyl, 4-chloro-2-methyl-phenyl, 4-cyano-phenyl, 4-iodo-phenyl, 4-isopropyl-phenyl, 4-methoxy-biphenyl-3-yl, 4-propyl-phenyl, 4-sec-butyl-phenyl, 4-tert-butyl-phenyl, 4-trifluoromethoxy-phenyl, 4-trifluoromethyl-phenyl, 5-chloro-2-

methoxy-phenyl, 5-methoxy-2-methyl-phenyl, 9-ethyl-9H-carbazol-3-yl, 9H-fluoren-2-yl, 9-oxo-9H-fluoren-1-yl, 9-oxo-9H-fluoren-2-yl, 9-oxo-9H-fluoren-4-yl, benzo[1,3]dioxol-5-yl, biphenyl-4-yl, indan-5-yl, naphthalen-2-yl; 2,4-dichloro-phenoxy)-phenyl, 2-phenoxy-phenyl, 3-phenoxy-phenyl, 4-phenoxy-phenyl; cyclohexylmethyl; or

R^{35} represents methyl; and R^{36} represents 4-acetyl-phenyl; (R)-1-phenyl-ethyl, benzyl; 3-chloro-phenyl; 4-chloro-phenyl; 4-fluoro-phenyl; 4-methoxy-phenyl; o-tolyl; m-tolyl or p-tolyl;

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, meso forms, geometric isomers,

prodrugs of compounds in which a prodrug forming group is present, as well as solvates and morphological forms and pharmaceutically acceptable salts thereof;

9. Novel compounds according to any one of claims 1 to 8 selected from the group consisting of

sodium [3-((E)-2-cyano-3-dibenzo[b,f]azepin-5-yl-3-oxo-propenyl)-indol-1-yl]-acetate;
{3-[(E)-2-(allyl-phenyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(phenethyl-phenyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(butyl-phenyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
(3-{(E)-2-cyano-2-[(2-cyano-ethyl)-phenyl-carbamoyl]-vinyl}-indol-1-yl)-acetic acid;
{3-[(E)-2-cyano-3-(10,11-dihydro-dibenzo[b,f]azepin-5-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid;
(3-{(E)-2-cyano-2-[(4-fluoro-phenyl)-methyl-carbamoyl]-vinyl}-indol-1-yl)-acetic acid;
{3-[(E)-2-cyano-2-(ethyl-phenyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-3-(6,11-dihydro-dibenzo[b,e]azepin-5-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(cyclohexyl-phenyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;
(3-{(E)-2-[(4-chloro-phenyl)-methyl-carbamoyl]-2-cyano-vinyl}-indol-1-yl)-acetic acid;
(3-{(E)-2-cyano-2-[(4-methoxy-phenyl)-methyl-carbamoyl]-vinyl}-indol-1-yl)-acetic acid;

{3-[(E)-2-cyano-2-(methyl-o-tolyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-diphenethylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
(3-{(E)-2-[(4-acetyl-phenyl)-furan-2-ylmethyl-carbamoyl]-2-cyano-vinyl}-indol-1-yl)-acetic acid;
(3-{(E)-2-[(4-acetyl-phenyl)-methyl-carbamoyl]-2-cyano-vinyl}-indol-1-yl)-acetic acid;
{3-[(E)-2-cyano-3-(3,4-dihydro-2H-quinolin-1-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid.
{3-[(E)-2-cyano-2-(methyl-phenyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;
(3-{(E)-2-[(3-chloro-phenyl)-methyl-carbamoyl]-2-cyano-vinyl}-indol-1-yl)-acetic acid;
{3-[(E)-2-(carboxymethyl-phenyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(benzyl-phenyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(3-benzoyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(2-ethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-methoxy-biphenyl-3-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-diphenylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
(3-{(E)-2-cyano-2-[2-(2,4-dichloro-phenoxy)-phenylcarbamoyl]-vinyl}-indol-1-yl)-acetic acid;
{3-[(E)-2-cyano-2-(2-methoxy-dibenzofuran-3-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(methyl-p-tolyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(5-chloro-2-methoxy-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(2-benzyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-3-(11,12-dihydro-6H-dibenzo[b,f]azocin-5-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(2-benzoyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-3-(2,3-dihydro-indol-1-yl)-3-oxo-propenyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(2-phenoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3,5-dimethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(3-bromo-4-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(2-methoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-(2-acetyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-7-methyl-indol-1-yl]-acetic acid.

10. Novel compounds according to any one of claims 1 to 8 selected from the group consisting of

{3-[(E)-2-cyano-2-(4-trifluoromethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
(3-{(E)-2-cyano-2-[methyl-((R)-1-phenyl-ethyl)-carbamoyl]-vinyl}-indol-1-yl)-acetic acid;
3-[(E)-3-(1-carboxymethyl-1H-indol-3-yl)-2-cyano-acryloylamino]-benzoic acid methyl ester;
{3-[(E)-2-cyano-2-(9-oxo-9H-fluoren-4-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-iodo-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(3-benzyloxy-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(benzyl-methyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(2-propyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
[5-bromo-3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
{3-[(E)-2-cyano-2-(3-methoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3-nitro-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3,5-dimethoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(9-ethyl-9H-carbazol-3-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(2,3-dihydro-benzo[1,4]dioxin-6-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(3-chloro-4-methoxy-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
4-[(E)-3-(1-carboxymethyl-1H-indol-3-yl)-2-cyano-acryloylamino]-benzoic acid ethyl ester;
{3-[(E)-2-(4-acetyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(2-isopropyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-tert-butyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(naphthalen-2-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(benzo[1,3]dioxol-5-ylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;

{3-[(E)-2-(2-bromo-4-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-cyano-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-bromo-3-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-5-fluoro-indol-1-yl]-acetic acid;
{3-[(E)-2-(biphenyl-4-ylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-isopropyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-chloro-2-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-5-methyl-indol-1-yl]-acetic acid;
{3-[(E)-2-cyano-2-(4-propyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(2,5-dimethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
3-[(E)-3-(1-carboxymethyl-1H-indol-3-yl)-2-cyano-acryloylamino]-4-methyl-benzoic acid methyl ester;
2-[(E)-3-(1-carboxymethyl-1H-indol-3-yl)-2-cyano-acryloylamino]-benzoic acid methyl ester;
{3-[(E)-2-(4-sec-butyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3-iodo-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-bromo-3-chloro-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-cyclohexylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
{3-[(E)-2-cyano-2-(3-fluoro-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-benzyloxy-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3,2'-dimethyl-biphenyl-4-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(5-methoxy-2-methyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
3-{benzyl-[(E)-3-(1-carboxymethyl-1H-indol-3-yl)-2-cyano-acryloyl]-amino}-propionic acid;
{3-[(E)-2-cyano-2-(9-oxo-9H-fluoren-2-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3-ethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(3,5-bis-trifluoromethyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-phenethylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;

[3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-6-fluoro-indol-1-yl]-acetic acid;
{3-[(E)-2-(4-bromo-2-methyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-trifluoromethyl-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(4-phenoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(indan-5-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(9H-fluoren-2-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(cyclohexylmethyl-carbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(4-butyl-phenylcarbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-(benzyl-carboxymethyl-carbamoyl)-2-cyano-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(3-phenoxy-phenylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
{3-[(E)-2-cyano-2-(9-oxo-9H-fluoren-1-ylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid.
[3-((E)-2-cyano-2-propylcarbamoyl-vinyl)-indol-1-yl]-acetic acid;
{3-[(E)-2-cyano-2-(3-methyl-butylcarbamoyl)-vinyl]-indol-1-yl}-acetic acid;
[3-((E)-2-cyano-2-phenylcarbamoyl-vinyl)-6-nitro-indol-1-yl]-acetic acid

11. A method for the treatment or prophylaxis of diseases mediated by CRTH2 comprising the administration to the patient a pharmaceutically active amount of a compound as claimed in any one of claims 1 to 10.

12. A method according to claim 11 wherein said amount is comprised between 1mg and 1000 mg per day.

13. A method according to claim 12 wherein said amount is comprised between 2 mg and 500 mg per day.

14. A method according to claim 13 wherein said amount is comprised between 5mg and 200 mg per day.

15. A process for the preparation of a pharmaceutical composition according to any one of claims 1 to 3 comprising mixing one or more active ingredient according to Formula I with inert carrier materials or excipients in a manner known per se.

Abstract

The invention relates to indol-1-yl-acetic acid derivatives and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and methods of treatment comprising administration of said compounds.